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CONTENTS.

Pending two years devoted to the development of the organization and sphere of the scientific work of the State Hospitals and their centre of scientific research—the Pathological Institute of the New York State Hospitals—the STATE HOSPITALS BULLETIN has served as medium of publication.

At present the plan and method of scientific investigation in the New York State Hospitals and Pathological Institute have become more defined, the lines of research of the several departments have become more completely organized, approaching more closely the original purpose of the foundation of a scientific centre of the New York State Hospitals—the plan of *correlation of sciences*, for the study of psychiatry.

This plan of scientific correlation in psychiatric research having during this period reached such a stage in its development as to unfold some definite results, it seems advisable to express the real character of our investigations, the outcome of this period of growth, in the title, more befitting the contents of the journal—ARCHIVES OF NEUROLOGY AND PSYCHOPATHOLOGY.

The ARCHIVES will contain studies on abnormal mental life and their neural concomitants, based on Psychology, Psychopathology, Experimental Physiology and Pathology, Cellular Biology, Pathological Anatomy, Comparative Neurology, Physiological Chemistry, Anthropology, and Bacteriology.

EDITORS.

DECEMBER, 1898.

PLATE I

NEURON ENERGY AND ITS PSYCHOMOTOR MANIFESTATIONS.

VOL. I 1898 No. 1

ARCHIVES OF NEUROLOGY AND PSYCHOPATHOLOGY

NEURON ENERGY AND ITS PSYCHOMOTOR MANIFESTATIONS.

(A PRELIMINARY COMMUNICATION).

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We intend here to set forth in a concrete diagrammatic form a theory that attempts to correlate the various general manifestations of psychomotor life with more or less definite physiological processes depending on the expenditure or restitution of neuron energy.

If this theory were perhaps to open some new lines in the study of abnormal mental and neural manifestations, or if only to stimulate a reconsideration of some of the old problems, its publication is not inappropriate.

In the first plan (Plate I), the parallelogram G M L H represents the total energy of the neuron. This total energy of the neuron is divided into three phases, viz.: Dynamic, Static and Organic.

By *dynamic energy* of the neuron is meant that part of energy which the neuron as an individual organism can dispose of in its relations to other neurons forming complex functioning organizations.

The dynamic energy is represented by the upper portion of the parallelogram A M L K.

By *static energy* is designated that portion of energy that is used only for the life maintenance of the neuron, both in relation to other neurons and to its own inner molecular constitution. Static energy cannot be drawn upon by the neuron in its functioning activity with other neurons without bringing about a state of disintegration.

Static energy is indicated by the diagram A F K I.

By *organic energy* is meant that energy contained in the tissues of the dead neuron, not as yet decomposed into their inorganic constituents.

The reader should not be confused at the very outset in the consideration of these three phases of neuron energy, by supposing that they are different kinds of energy, in the sense of being distinct entities. This is not so. They merely represent three progressive phases or stages of the same process of neuron activity.

Liberation of neuron energy is correlative with *active* psychic or physical manifestations. Hence states of the nervous system corresponding to liberations of energy we have designated as *waking states*. *Restitution* of expended energy or *arrest* of liberation of neuron energy go hand in hand with *passive* conditions of the nervous system; hence states of restitution or arrest of energy we have termed collectively *sleeping states*.

In the first diagram, this correlation is followed out in the direction of the arrows. The downward arrow indicating successive levels of liberation of energy, corre-

sponds to a similar downward arrow on the right hand side of the diagram, which indicates the course and progress of the waking states running parallel to the process of liberation of energy. The arrows on the left hand side of the diagram illustrate the physiological and pathological processes at work in the cycles of expenditure and restitution of energy, while the right hand side of the diagram indicates by its arrows the concomitant psychomotor manifestations—the waking and sleeping states.

The ascending arrow of restitution of energy corresponds to the ascending arrow on the right indicating the parallel psychomotor sleeping states. The descending arrows indicate physiological and pathological processes of liberation of energy and also their concomitant psychomotor waking states. Ascending and descending mean the rise and fall of the amount of energy, taking the upper level of dynamic energy as the starting point. Briefly stated, *descent* means *liberation* of energy with its concomitant psychomotor waking states. *Ascent* means *restitution* of energy with its parallel sleeping states.

The cycles in dynamic energy correspond to the physiological manifestations of the nervous system in the activity and rest of the individual in normal daily life. Concomitant with the expenditure of dynamic energy of the neurons, the individual passes through the active normal waking state, and hand in hand with the restitution of this expended dynamic energy, he passes through the sleeping state of normal daily life.

When, however, in the expenditure of energy, the border line or margin, A K, is crossed, dynamic energy is used up and static energy is drawn upon. The border line that separates the normal physiological from the abnormal or pathological psychomotor manifestations is stepped over.

Static energy may in its turn be divided into two phases according to the nature of the process of liberation of neuron energy. As long as the process of liberation of energy effects only a *dissociation* of systems of neurons the correlative psychomotor manifestations fall under the category of *psychopathies*. If, however, the process of liberation affects the neuron itself, bringing about a *disintegration* of its constituent parts compatible with restitution, the correlative psychomotor manifestations fall under the category of *neuropathies*. This process of disintegration, equivalent to cell degeneration in the pathoanatomical sense, may end in death, in the dissolution of the neuron itself.*

By *psychopathies*, then, we designate the pathological phenomena of *psychic disaggregation* correlative with the state or processes of dissociation within clusters or constellations of neurons, *the neuron itself remaining undamaged.*†

By *neuropathies*, we mean to indicate a group of psychophysical manifestations, running parallel to fluctuations of static energy and accompanied *by organic changes in the neuron*

We may now turn to the larger and more complete schema.

The second chart (Plate II) is a further development of the first plan (Plate I). In it the pathological processes and their psychomotor concomitants are given in more or less provisional detail.

The *physiological* processes and corresponding psychomotor manifestations in the fluctuations of the *dynamic energy* hardly need, in the present communication, any further explanation, except possibly to indicate that

* Vide Sidis "Psychology of Suggestion." Ch. XXI, p. 214; Ch. XXIII, p. 234.

† The pathological phenomena of dissociation are discussed in full in "The Psychology of Suggestion."

dynamic energy is represented as expended and recruited by small or possibly infinitesmal differentials and increments. This is indicated by the parallel lines drawn across the rectangle representing dynamic energy, this energy falling or rising to different levels. Each of these increments is indicated by a fraction of the total energy, represented by the numerator *e* and the denominator *n*. The energy is assumed as drawn off, or recruited at any part of the whole rectangle by n^{ths} of the total amount.

Passing across the border line A K of the cyclic fluctuations corresponding to physiological metabolism constituted by the processes of catabolism and anabolism, fluctuations in the upper levels of the static energy of the neurons, are met with. Here we step over the catalytic threshold.

The physical processes occurring in the neuron, corresponding to these changes in the upper levels of the static energy, are no longer physiological, but pathological, and correspond to catalysis and synthesis.

Catalysis corresponds to liberation of the upper levels of static energy, and is accompanied by *retraction of aggregates of neurons*, bringing about the phenomena of psycho-physiological dissociation. Restitution of the energy expended in the catalytic process is accompanied by *expansion* or *synthesis* of the neurons which are again able to transmit or receive impulses in the particular aggregate to which they belong.* An arrest or halt after the expenditure of energy in these upper static levels, corresponds again to a state of retraction of the neuron or catalysis.†

On the right hand side of the diagram, concomitant

* For further details see Sidis "Psychology of Suggestion," Chap. XXI, XXIII.

† Apathy's "anastamosis" theory may hold true of the nervous system of the invertebrates, but not of the cerebro-spinal system and certainly not of the association areas. This topic will form the subject of a separate work.

with the processes of catalysis or synthesis of the neuron, we find corresponding pathological states of psychic disaggregation and aggregation: *psychopathic waking states* or states of mental dissociation going hand in hand with *catalysis*, and *psychopathic sleeping states* with the process of *synthesis*.

In the second column, on the right hand side of the diagram, a general outline is given of the detailed manifestations of the psychopathic waking states. These are given in the sequence in which they occur, as far as we can determine in the present writing, according to the progression of the catalytic process passing from the very highest constellations of neurons which the nervous system possesses, down through lower and lower associations and finally to groups of neurons.*

In the third column to the right of the central rectangle in the diagram are given some of the specific manifestations of the neuron associations during the psychopathic sleeping state, when the upper levels of static energy have reached the maximum of their expenditure, and ascend toward the normal physiological level by the process of restitution of energy.

These cycles in the rise or fall of energy are always indicated by the direction of the smaller arrows on either side of the central rectangle, representing the total energy of the neuron.

Psychopathic manifestations correspond to the processes of catalysis and synthesis of the neurons, or to an arrest in the liberation of energy after catalysis has progressed to a certain degree.

Passing now beyond the catalytic margin in the expenditure of static energy of the neuron, we may consider

* Vide Sidis "Psychology of Suggestion," Chap. XX and XXI.

the further expenditure of static energy. Here we step over the cytolytic threshold. The pathological process corresponding to expenditure of the levels of static energy beneath the cytolytic threshold is termed *cytolysis* of the neuron, which means cell-resolution. At this point organic and structural changes are found in the neuron, more particularly in the character of the cytolymph.* We have here the *initial stages of the process of neuron degeneration*, and the term cytolysis indicates such phases of parenchymatous degeneration of the neurons which may lead either to restitution or destruction. Cytolysis, therefore, embraces the phases of organic degeneration of the neurons up to, but not beyond the border line of destruction in the progression of this degeneration.

The regeneration of these degenerative changes in the cell, not over-stepping the limits of destructive alterations in the neuron, is termed *cytothesis*. It is the reverse of cytolysis.

Corresponding again to the pathological processes of cytolysis and cytothesis, going hand in hand with fluctuations in the lower levels of static energy, are the concomitant *neuropathic* waking and sleeping states with their psychomotor manifestations.

Broadly speaking, psychopathies run parallel to the phenomena of retraction and expansion of aggregates of neurons, while neuropathies are concomitant with actual degeneration of the neuron, especially of its cytolymph.

The expenditure of organic energy is accompanied with cell-destruction or *cytoclasis*.† Cytoclasis is the destructive outcome of degeneration of the neurons—parenchymatous degeneration of the nervous system, acute or chronic.

* For further details of these processes see van Gieson "The Toxic Basis of Neural Diseases," begun in a previous issue of the STATE HOSPITALS BULLETIN.

† Vide van Gieson, "Toxic Basis of Neural Diseases."

There can be neither waking nor sleeping states below the cytolytic margin, as the neuron is dead.*

In setting down the specific symptomatic expressions of the several psychopathic and neuropathic sleeping and waking states, it is impossible, in many instances, to draw sharp lines of division between the two sets. They are necessarily put down in a general way, and more or less provisionally as an attempt to analyze psychomotor phenomena manifested in abnormal nervous and mental life on a tangible basis of fluctuations of neuron energy.

The difficulty of sharply defining abnormal waking and sleeping states of the nervous system lies in the fact that in the same individual one part of the nervous system is in the process of restitution and is in a sleeping state, while another portion is in the process of expending energy and is in a waking state.

The reader should also be guarded from receiving the impression that sleeping stadia of the nervous system necessarily go hand in hand with a progressive upward rise of the process of energy restitution. It is always to be remembered that the downward process in the liberation of energy is not necessarily followed by the opposite cycle of restitution of energy. The process may halt, or, strictly speaking, *oscillate*, at some particular level, as at B, C, or D, (in the central rectangle) when a sleeping state is liable to predominate, because from the very nature of pathological metabolism the ascending processes are slower in their course than the descending processes. The liberation process may then, without rising, descend to a still deeper level, as at E. It may then rise to C, and fall back to D, and so on through an almost indefinite

* Vide Sidis "Psychology of Suggestion," pp. 214, 232.

series of halts,—upward and downward fluctuations. This ought to make clear our conception of the progression of the sleeping and waking states. Thus, the pathological process and symptoms concurrent with the expenditure of successive levels of static energy may descend and continually go down deeper into the psychopathic and neuropathic realms of psychomotor manifestations. Finally, the descent may be so great that the liberation of energy corresponds to the destruction of the nerve cell, and the disease becomes permanent. The earliest manifestations of general paresis, for instance, are those corresponding to the liberations or restitutions of the uppermost levels of static energy, but finally the process of liberation reaches such a depth that the disease becomes destructive. *Psychopathies may therefore become neuropathies, and neuropathies may in their turn progress to the cytoclastic type and result in an absolute and irrevocable loss of function of the neuron.**

The fluctuations of energy again may be such as to take a pronounced alternating or cyclical type, and herein, we believe, is a rational explanation of the circular insanities. *The active periods of the circular insanities belong to waking states, and the passive periods are sleeping states of the nervous system.* This holds true not only of psychopathic, but also of neuropathic circular states—states of alternating delirium and coma such as are found in the acute general somatic diseases that involve the nervous system. The active delirium is placed on the side of the vertical line to be included in the neuropathic waking states, and the passive or comatose alternation of the neuropathic psychic manifestations is set down among the neuropathic sleeping states.

* Vide Sidis "Psychology of Suggestion," Chap. XXIII, pp. 215, 232.

It should be remembered that the psychopathic cyclic insanities may not at all remain fixed where they begin in the psychopathic realm, they may descend into the neuropathic domain. In the consideration of this second chart in general, it is always to be held in mind that the order in which these phenomena are set down in the psychopathic and neuropathic states is an order both serial and progressive and no particular set of symptoms is to be considered as fixed in this scale, except as to its course and origin. Thus psychopathic may descend into neuropathic waking states and these again into the domain of destruction of the nerve cell. On the other hand, neuropathic sleeping states may rise to the level of psychopathic sleeping states. Cytoclastic states, however, cannot rise,. there can be no restitution because the neuron is destroyed. If *any recovery from cytoclasis does occur, it is because of a compensatory action of other neurons and an education on the part of new neurons to assume the functions lost by their destroyed associates.*

It must be distinctly understood, that while the parenchymatous degeneration associated with these several pathological processes begins as a cytolytic lesion, compatible with restitution and recovery of the neuron, it may pass on to the destructive state. No one can say, in treating of these nervous diseases generically, whether they may become cytoclastic or remain cytolytic and susceptible of recovery. The determination of such a question must be sought out in the special conditions of each particular case.

Furthermore, the important fact must be kept clearly in mind that various groups and systems of neurons may reach different degrees of disaggregation and degeneration, may be simultaneously in different stages of the one continuous descending pathological process of energy

liberation. A community, cluster or constellation of neuron aggregates, *A*, may be in the upper levels of the psychopathic state; another, *B*, in the deeper levels of the same state; *C* and *D* in different levels of the neuropathic state, while *E* and *F* may have descended to the levels of cytoclasis. Such a complexity of phenomena is well illustrated in general paresis. Thus the fact that various systems of neurons are often in different stages of disaggregation or degeneration frequently gives rise to a mixed and complex symptomatology, the malady presenting symptoms (psychomotor manifestations) belonging to different stages in the descending pathological process. The disease, however, may still be characterized as *psychopathic*, if *most* of the neuron aggregates are in the psychopathic state; it may be designated *neuropathic*, if *most* of the neuron aggregates are in the neuropathic state; it may be termed *cytoclastic*, if *most* of the neuron aggregates involved in the process, have reached the destructive stage of cell degeneration. The symptomatology of psychomotor manifestations may thus vary endlessly, like the figures in the kaleidoscope. The *symptomatic side of disease is a function of* LOCATION, NUMBER *and* DEGREE. *It depends on the location and number of neuron aggregates involved and on the stage or degree of the descending pathological process.*

We must be clear in reference to some other points.

First, neuron energy may be liberated even in the dynamic and static levels not as psychomotor manifestations, but as heat, electricity, etc.

Secondly, the dissipation of *organic* energy of the neuron takes the form of chemical energy in the dissolution of the bodies composing the cyto-reticulum or in giving rise to heat or electric currents. These two latter forms of energy are of no special interest in connection with psycho-

motor manifestations, they fall outside the domain of *functional* energy of the neuron, the subject matter of this communication. This liberation of non-nervous energy from destruction of the cyto-reticulum is the reason of the prolongation of the descending arrow beyond the cytolytic margin.

Thirdly, we do not believe that a sleeping state of the nervous system can occur without an antecedent waking state. The patient may not come under observation, during this antecedent waking state, and as a matter of fact rarely does in those psychopathic waking stages where the attack is acute and the liberation process is of a very short duration. The active waking state corresponding to liberation of energy, preceding what is supposed to be the primary depressed state, may be sudden, fleeting, unobtrusive, but it must exist. *An individual cannot be precipitated into a sleeping state without having gone through an antecedent active or waking state.*

To complete this chart a whole domain of psychomotor manifestations is requisite, namely, that corresponding to the fluctuations of neuron energy, containing the mixed phenomena of simultaneous waking and sleeping states. These states, as well as many other conditions, require a careful experimental investigation from the standpoint of our theory.

Finally, it should be noted that the division lines, such as lie between the cycles of physiological and the subdivisions of the cycles of pathological metabolism, are rather relative. One process directly and continuously passes over into the other; thus catalysis is the forerunner of cytolysis, and cytolysis may become the forerunner of cytoclasis. *All of them, however, are stages in the one continuous process of liberation of neuron energy.**

* Vide Sidis "Psychology of Suggestion," pp. 214, 215, 232.

The various nervous and mental diseases are generally considered as separate things. Each disease is assumed as standing by itself, an independent clinical entity, an "Anundfürsichsein." This view is metaphysical, although it would seem that nothing is so far removed from metaphysics as medical science. Now, as a matter of fact, *diseases are not entities, but processes. Particular sets of symptoms characterizing different clinical pictures of nervous and mental diseases form stages in the one continuous process of liberation of neuron energy of the specially affected neuron aggregates.*

This one continuous process of liberation of neuron energy may cover the life of a single individual or may extend over the life-history of many generations. The continuous descending pathological process may spread out in time and space, may extend over a long duration of time and embrace a great number of individuals. The tide of neuron energy may ebb away gradually, leaving each succeeding generation on a lower stage and deeper level in the continuous process of neuron disaggregation and degeneration, thus giving rise to the different stages and manifestations of *congenital degeneracy*. Many of the so-called degeneracies and the congenital diseases of the nervous system arise, we believe, in this way.

In the higher parts of the nervous system pathological processes begin in catalysis, on further descent pass into cytolysis, and if continued further terminate into cytoclasis. In these regions *catalysis, cytolysis, cytoclasis, are the three progressive descending stages in the complete cycle of pathological processes.* In the lower and lowermost neural segments, however, pathological processes may lack catalysis and begin in cytolysis.

The processes of liberation and restitution of neuron

energy may be symbolically represented in the following formulæ:

Let D represent the physiological or dynamic energy of the neuron, S its static, and R its organic energy, then D+S+R=E, or total energy of neuron; that is

$$D+S+R=E \quad (1).$$

Let $\frac{e}{n}$ be the differential (see Plate II, rectangle K A M L) liberated by each successive or progressive increment of stimulus, then a progressive series arises, the summation of which will be equal to D, or

$$D-(\tfrac{e}{n}+\tfrac{e}{n}+\tfrac{e}{n}+\tfrac{e}{n}+\tfrac{e}{n}+\ldots\ldots\tfrac{e}{n}+\tfrac{e}{n})=0 \quad (2)$$

This represents a progressive descending series in the course of neuron activity of the physiological waking state corresponding to the process of catabolism. If we subtract D or the sum of the descending progressive series from E, or total energy, we have static and organic energies or

$$E-(\tfrac{e}{n}+\tfrac{e}{n}+\tfrac{e}{n}+\tfrac{e}{n}+\tfrac{e}{n}+\ldots\ldots\ldots\tfrac{e}{n}+\tfrac{e}{n})=S+R \quad (3)$$

Having descended and reached S, the process of liberation may continue, but at this point it passes into the regions of *pathological waking states*. The process of liberation continues in the same way by $\frac{e}{n}$ decrements.

Now S may be divided into two separate but continuous series representing two stages of the pathological waking state in the progressively descending scale of liberation of neuron energy. The first series corresponds to catalysis, the second to cytolysis.

The process of liberation of organic energy of the neuron R corresponds to cytoclasis.

If the static energy liberated by catalysis be designated by C, the energy liberated by cytolysis by C_1, and the

organic energy set free by cytoclasis by C_2, then we have the following formulæ:

$$C-(\tfrac{e}{n}+\tfrac{e}{n}+\tfrac{e}{n}+\tfrac{e}{n}+\ldots\ldots\tfrac{e}{n}+\tfrac{e}{n})=0 \quad (4)$$ Catalytic margin.

$$C_1-(\tfrac{e}{n}+\tfrac{e}{n}+\tfrac{e}{n}+\tfrac{e}{n}+\ldots\ldots\tfrac{e}{n}+\tfrac{e}{n})=0 \quad (5)$$ Cytolytic margin.

$$C_2-(\tfrac{e}{n}+\tfrac{e}{n}+\tfrac{e}{n}+\tfrac{e}{n}+\ldots\ldots\tfrac{e}{n}+\tfrac{e}{n})=0 \quad (6)$$ Cytoclastic terminus.

These formulæ express respectively the limits of liberation of energy of the three descending pathological processes.

Adding equations (4), (5), (6) together, we have:

$$(C+C_1+C_2)-[(\tfrac{e}{n}+\tfrac{e}{n}+\tfrac{e}{n}+\ldots\ldots\tfrac{e}{n}+\tfrac{e}{n})+(\tfrac{e}{n}+\tfrac{e}{n}+\tfrac{e}{n}+\ldots\ldots\tfrac{e}{n}+\tfrac{e}{n})+(\tfrac{e}{n}+\tfrac{e}{n}+\tfrac{e}{n}+\ldots\ldots\tfrac{e}{n}+\tfrac{e}{n})]=0 \quad (7)$$

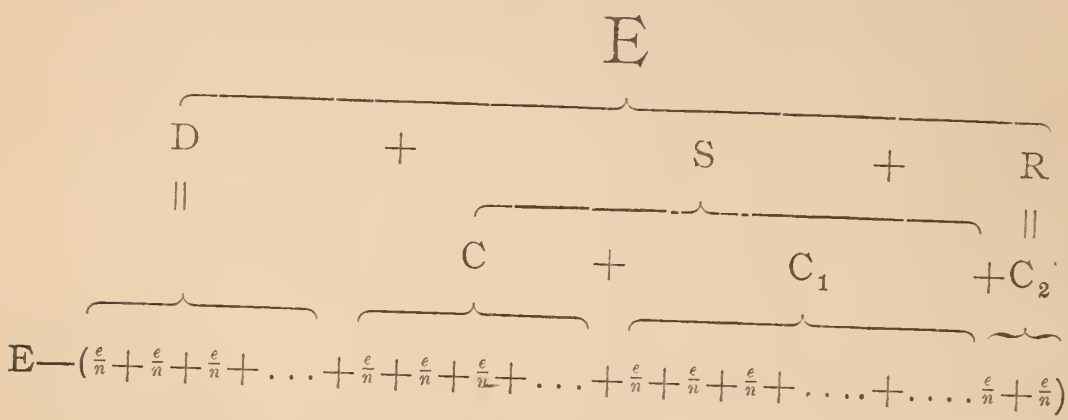
With the final decrement of equation (5) we reach the functional zero point or cytolytic margin and with the final term of equation (6) we reach the absolute zero point, the terminus of liberation of energy. The cytolytic margin indicates the end of the expenditure of *nervous* or *functional* energy; the cytoclastic terminus marks the close of the residual or *non-nervous* energy of the neuron. The lowest limit in the descending process of energy dissipation is reached at the cytoclastic terminus of the total cell energy. This terminus may be represented in the following formulæ:

$$E-D-S-R=E-D-(C+C_1+C_2)=0 \quad (8) \quad \text{or,}$$

$$E-[(\tfrac{e}{n}+\tfrac{e}{n}+\tfrac{e}{n}+\ldots\ldots\tfrac{e}{n}+\tfrac{e}{n})+(\tfrac{e}{n}+\tfrac{e}{n}+\ldots\ldots\tfrac{e}{n}+\tfrac{e}{n})+(\tfrac{e}{n}+\tfrac{e}{n}+\tfrac{e}{n}\ldots\tfrac{e}{n}+\tfrac{e}{n})+(\tfrac{e}{n}+\tfrac{e}{n}+\tfrac{e}{n}\ldots+\tfrac{e}{n}+\tfrac{e}{n})]=0 \quad (9)$$

Recapitulating the whole process of the continuous progressive *descending* series of liberation of nervous cell

energy from the *minimum* to the *maximum* limit, we have the following formula:



Each term in the descending series of liberation of functional or nervous energy manifests itself as a waking state, physiological, *i. e.*, catabolic; or pathological, *i. e.*, catalytic and cytolytic, according to the depth of the descent.

Having formulated the descending series of liberation of nerve-cell energy, we turn now to the formulation of the process of restitution of energy which takes place in an *ascending* series.

If in the equation (2) the number of terms be M, the summation of them will give $M\frac{\varepsilon}{n}$, then in the complete integration of the ascending series concomitant with the anabolic physiological sleeping state we have:

$$D=M\frac{\varepsilon}{n} \quad (11)$$

In a similar way we may integrate the pathological series in the ascending scale of restitution, namely, equations (4) and (5). The summation of equation (4) which we may suppose as having M_1 terms in the ascending series of the synthetic sleeping state will give us the following formula:

$$C=M_1\frac{\varepsilon}{n} \quad (12)$$

The summation of equation (5) which we may suppose

as having M_2 terms in the ascending series of the cytothetic sleeping state will give the following formula:

$$C_1 = M_2 \tfrac{e}{n} \quad (13)$$

The series of cytoclasis cannot be integrated as restitution, from the very nature of the destructive character of the cytoclastic process, is impossible.

Thus far we have dealt with *complete* cycles in the descending scale of liberation of energy concomitant with waking states and the ascending scale of restitution concomitant with sleeping states. Each cycle, however, may be incomplete, may stop and oscillate at any point in the scale of the series. Thus the ascending process of integration or restitution of energy may be only $\frac{e}{n}$, or $2\frac{e}{n}$, or $3\frac{e}{n}$,.....or $(M-1)\frac{e}{n}$ of the expended nervous energy. The restitution of these increments may be characterized as *positive* and indicated by (+).

The same holds true in the case of the process of loss or liberation of neuron energy, it may descend and reach any point in the descending series. The dynamic energy D, for instance, may lose the decrement, $\frac{e}{n}$, or decrements $2\frac{e}{n}$, $3\frac{e}{n}$.....$(M-1)\frac{e}{n}$, $M\frac{e}{n}$, and become $D-\frac{e}{n}$, $D-2\frac{e}{n}$, $D-3\frac{e}{n}$.....$D-(M-1)\frac{e}{n}$, $D-M\frac{e}{n}$. These losses or decrements of liberation of energy may be characterized as *negative* and indicated by (−).

Since the descending process of liberation of cell energy is divided into four stages, one merging into the other, namely, the catabolic, the catalytic, the cytolytic and the cytoclastic, and since the reverse series of the ascending process is divided into three stages, one passing into the other, namely, the cytothetic, the synthetic and the anabolic, it would be well to co-ordinate these processes and their stages and represent them by the following comprehensive formula:

WAKING STATES.

(14)

Catabolism.	*Anabolism.*
D	$M^{\frac{e}{n}}$
$D—^{\frac{e}{n}}$	$(M-1)^{\frac{e}{n}}$
$D—2^{\frac{e}{n}}$	$(M-2)^{\frac{e}{n}}$
$D—3^{\frac{e}{n}}$	$(M-3)^{\frac{e}{n}}$
$D—4^{\frac{e}{n}}$	$(M-4)^{\frac{e}{n}}$
. . . . .	. . . . .
. . . . .	. . . . .
. . . . .	. . . . .
$D—(M-1)^{\frac{e}{n}}$	$^{\frac{e}{n}}$
$D— M^{\frac{e}{n}}$	0

Liberation of Dynamic Energy. — Restitution of Dynamic Energy.

PHYSIOLOGICAL.

(15)

Catalysis.	*Synthesis.*
C	$M_1{}^{\frac{e}{n}}$
$C—^{\frac{e}{n}}$	$(M_1-1)^{\frac{e}{n}}$
$C—2^{\frac{e}{n}}$	$(M_1-2)^{\frac{e}{n}}$
$C—3^{\frac{e}{n}}$	$(M_1-3)^{\frac{e}{n}}$
$C—4^{\frac{e}{n}}$	$(M_1-4)^{\frac{e}{n}}$
. . . . .	. . . . .
. . . . .	. . . . .
. . . . .	. . . . .
$C—(M_1-1)^{\frac{e}{n}}$	$^{\frac{e}{n}}$
$C— M_1{}^{\frac{e}{n}}$	0

Liberation of Upper Levels of Static Energy. — Restitution of Upper Levels of Static Energy.

PSYCHOPATHIC.

(16)

Cytolysis.	*Cytothesis.*
C_1	$M_2{}^{\frac{e}{n}}$
$C_1—^{\frac{e}{n}}$	$(M_2-1)^{\frac{e}{n}}$
$C_1—2^{\frac{e}{n}}$	$(M_2-2)^{\frac{e}{n}}$
$C_1—3^{\frac{e}{n}}$	$(M_2-3)^{\frac{e}{n}}$
$C_1—4^{\frac{e}{n}}$	$(M_2-4)^{\frac{e}{n}}$
. . . . .	. . . . .
. . . . .	. . . . .
. . . . .	. . . . .
$C_1—(M_2-1^{\frac{e}{n}})$	$^{\frac{e}{n}}$
$C_1— M_2{}^{\frac{e}{n}}$	0

Liberation of Lower Levels of Static Energy. — Restitution of Lower Levels of Static Energy.

NEUROPATHIC.

SLEEPING STATES.

PHYSIOLOGICAL.

Cytolytic Margin. (Exhaustion of Cyto-lymph).

Cytoclasis.
C_2
$C_2—^{\frac{e}{n}}$
$C_2—2^{\frac{e}{n}}$
$C_2—3^{\frac{e}{n}}$
$C_2—4^{\frac{e}{n}}$
. . . . .
. . . . .

Liberation of Non-Nervous Energy—Heat, Chemical Energy.

Cytoclastic Terminus of Neuron Energy.

(Destruction of Cyto-reticulum).

Formulæ (14), (15) and (16) illustrate the phases of seeming arrests, but really of oscillations in the progression of the processes of liberation or restitution of energy. In catalysis, for instance, liberation of energy may oscillate at the level, $C-\frac{e}{n}$, when a sleeping state may predominate. The catalytic process may then descend to a lower stage of the series, $C-4\frac{e}{n}$, and during the descent there is a waking state. If an oscillation occurs at the level, $C-4\frac{e}{n}$, a sleeping state again preponderates. Certain cases of cyclical insanity manifesting alternations of waking and sleeping states with slight or no restitution of energy may serve as a case in point. The process of liberation of energy has slipped from one level to a deeper one, thence to a still deeper level, oscillating for a period at each of these levels. In the same way, in formula (15), in the right hand column of series, corresponding to the synthetic process, we may have a similar symbolical illustration of oscillatory periods in the restitution of energy.

The upper levels of static energy in any particular individual may be reduced to the catalytic margin, the process of disintegration may become arrested at this point and the reverse process of synthesis may begin; the process of restitution of energy may rise by $\frac{e}{n}^{\text{ths}}$. The recuperation of the energy corresponding to synthesis may rise say to $(M_1-4)\frac{e}{n}$ (formula 15, right hand column); after oscillating there a while it may rise to a higher level of the series such as $(M_1-1)\frac{e}{n}$, and so on until all the upper levels of static energy expressed by the final member of the ascending series, $M_1\frac{e}{n}$, are recovered. The individual has recovered all the upper levels of his static energy and is on the way to become normal; he is about to step across the border line into the realm of the normal physiological sleeping state.

We may conclude this brief preliminary communication with a few laws relating to the metabolic processes of neuron activity:

(I)—*Catalysis stands in direct and synthesis in inverse ratio to the number of disaggregated neuron associations.*

(II)—All other conditions remaining the same, *the instability of a cell aggregate is proportionate to the* number *and* complexity *of its associative functioning groups.**

(III)—*The stability of a neuron aggregate is proportionate to the* frequency *and* duration *of its associative activity.*†

(IV)—*The instability of a neuron aggregate is proportionate to the* frequency *and* duration *of the* interruptions *in its functioning activity.*‡

(V)—*The mass of formed metaplasm granules*‖ *stands in direct ratio to the intensity of cytolysis and in inverse ratio to the progress of cytothesis.*

* See Sidis, Psychology of Suggestion, p. 212.

† Ibid, p. 210.

‡ For further details, particularly in relation to the many forms of psychopathies, see the second part of The Psychology of Suggestion, especially Chapters XX, XXI, XXII, XXIII.

‖ "Metaplasm granules" is a term given by one of us, in order to be more explicit about the significance of the commonly called pigment granules of the ganglion cell. Metaplasm granules are the lifeless particles in the neuron, excreted from it; they are waste products attending the liberation of energy, especially pathological liberations, from the cytolymph; hence we think that the volume of these metaplasm granules is a measure of the declining capacity of the cytolymph to elaborate and liberate neuron energy. Vide van Gieson, "Toxic Basis of Neural Diseases."

NEURON ENERGY AND ITS PSYCHOMOTOR MANIFESTATIONS.

TOTAL ENERGY OF NEURON.

DYNAMIC. STATIC. ORGANIC.

CYCLE OF PHYSIOLOGICAL METABOLISM.

CATABOLISM (OF THE NEURON)
Liberation of dynamic energy of the neuron.

ANABOLISM (OF THE NEURON)
Integration—Restitution of liberated dynamic energy.

Catabolic Margin. (Limit of Catabolic Process.)

Catalytic Threshold.

CYCLES OF PATHOLOGICAL METABOLISM.

DISAGGREGATION AND AGGREGATION OF NEURONS.

CELL RESOLUTION AND RESTITUTION.

Cell Destruction.

DISSIMILATIVE RETRACTION
Causing dissociation or disaggregation of constellations, communities, clusters, systems and groups of neurons in the dissociation areas.* = NEURON CATALYSIS
Liberation of static energy.

DENDRITIC EXPANSION.
Forming associations and aggregations in inverse order of disaggregative process, viz.: Of groups, systems, clusters, communities and constellations. = NEURON SYNTHESIS
Integration of static energy liberated by the catalytic process.

Catalytic Margin. (Limit of Catalytic Process.)
Cytolytic Threshold.

CELL RESOLUTION.
Progressive parenchymatous degeneration of the neuron, of the cytolymph only (the storehouse of energy). = NEURON CYTOLYSIS
Further progressive liberation of static energy beyond catalysis.

CELL RESTITUTION.
Progressive restitution of cytolymph. Reconstruction of chemical compounds resolved by the cytolytic process. = NEURON CYTOTHESIS
Integration of static energy liberated by the cytolytic process.

RESTITUTION OF ENERGY OF THE NEURON.

LIBERATION OF ENERGY OF THE NEURON.

Cytolytic Margin. (Limit of Cytolytic Process.)
Cytoclastic Threshold.

CELL DESTRUCTION.
Progressive degeneration of the organic and formed structures of the neuron. Degeneration and dissolution of cytoreticulum of the neuron. No restitution = CYTOCLASIS (OF THE NEURON)
Progressive liberation of organic energy.

DEATH OF NEURON

*See Sidis "Psychology of Suggestion," Part II, Chapters XX, XXI, XXII, XXIII.

WAKING STATES. SLEEPING STATES. NORMAL. PSYCHOPATHS. ABNORMAL. NEUROPATHS.

—PHYSIOLOGICAL WAKING STATES.

—PHYSIOLOGICAL SLEEPING STATES.

Physiological Margin. (Limit of Sense of Fatigue.)
Psychopathic Threshold.

PSYCHOPATHIC WAKING STATES.

PSYCHOPATHIC SLEEPING STATES

Psychopathic Margin.
Neuropathic Threshold.

NEUROPATHIC WAKING STATES.

NEUROPATHIC SLEEPING STATES.

Neuropathic Margin

WAKING PHASE OF DAILY NORMAL LIFE.

Psychopathic weakening of discriminatory constellations and concomitant impressionability of the sub-conscious Dream States, auto-suggestiveness, somnambulism

PSYCHOPATHIC EXCITEMENT due to action of stimuli passing beyond physiological limits. Loss of psychic inhibition and self-control. Beginnings of abnormal mental and moral irresoluteness, irritability of temper.

MENTAL AND NERVOUS SYMPTOMS OF OVER-FATIGUE.—Insomnia, neurasthenia, irritability, aprosexia, weakening of self-discipline, childishness, emotionalism.

PSYCHOPATHIC WILL DISTURBANCES.—Aboulia: localized, systematized, general.

HYPNOID, HYPNOIDIC, HYPNOIDAL AND HYPNONERGIC STATES.—Phenomena of autokinetic writing, crystal gazing, shell hearing, &c., psychopathic illusions and hallucinations.

PSYCHOPATHIC MEMORY DISTURBANCES.—Amnesia: simple, recognitive, synthetic, special, localized, sensory, motor, periodic, &c. Forms of psychopathic sensory amnesia, aphasia, psychopathic sensory apraxia.*

PSYCHOPATHIC SENSORY DISTURBANCES.†

PSYCHOPATHIC MOTOR DISTURBANCES.‡

PSYCHOPATHIC TROPHIC, VASO-MOTOR AND VISCERAL DISTURBANCES.§

PSYCHOPATHIC SUB-MANIACAL STATES.‖

PSYCHOPATHIC MANIACAL STATES.¶

PSYCHOPATHIC CONVULSIVE STATES.—*Sudden* dissociation in consciousness bringing about low and even elementary sub-conscious states due to a concomitant sudden disaggregative process of retraction of constellations extending to elementary groups of neurons. Such states are to be found in idiopathic epilepsy, psychic equivalent of epilepsy, the phenomena of so-called hystero-epilepsy and in the obscure uninvestigated states known as "psychic epilepsy."**

NEUROPATHIC MANIA—DELIRIUM.

Progressive phases of severity of the *delirium of the general somatic diseases.* Toxic delirium, neuropathic (cytolytic) delirium of the acute infectious diseases and accompanying the action of the several classes of pathogenic poisons (extrinsic poisons, bacterial toxins, autogenous poisons, protozoal toxic poisons and combinations of these). Neuropathic (cytolytic) manie, which takes place gradually, of increasing degrees up to ..... hyperacute mania and thence to ..... hyperacute mania and delirium grave.

All neuropathic waking states corresponding to excitation of neuron in acute parenchymatous degeneration not passing beyond the cytoclastic or destructive phase, *e.g.*, delirium, insolation, delirium tremens, delirium of typhoid fever, pneumonia, &c., &c. Acute parenchymatous degeneration of the neuron associated with acute diffuse inflammation of nervous system, *e.g.*, Landry's paralysis, rabies.

Lesions beginning as cytolysis, but complicated with cytoclasis accompanied or not by acute or chronic diffuse inflammation, or acute exudative inflammation.

Acute parenchymatous degeneration of nervous system going on to cell destruction (insolation), terminal dementia, experimental thyropravia. Acute diffuse inflammation of the nervous system passing over into cell destruction (rabies), Landry's paralysis.

Destructive and necrotic lesions of the nervous system in general due to chronic parenchymatous degeneration of nervous system, *e.g.*, tabes dorsalis, amyotrophic lateral sclerosis, terminal dementia.

Acute exudative inflammation of nervous system (acute myelitis).

Chronic diffuse inflammation of nervous system (general) paresis), terminal dementia.

SLEEPING STATES OF NORMAL DAILY LIFE.

DREAM STATES.
The sleeping state in hypnotism, disaggregation of the upper constellations of neurons.

Psychopathic sleeping states of various gradations and intensity up to the level of the physiological sleeping state, the passive and exhaustive phases of neurasthenia.

Beginnings of psychopathic melancholia.

Deeper levels of psychopathic melancholia

Depressive psychopathic states.

Psychopathic passive sleeping states of narcosis—toxic narcosis.

Passive trance conditions.

Melancholia of increasing degree

Lethargic states.

Psychopathic paroxysmal sleep states of various durations.

Hypnoleptic states.***

Deeper psychopathic sleeping states of toxic narcosis.

Psychopathic narcolepsy.

Morbus hypnoticus.

Psychopathic coma.

Psychopathic melancholia of deeper levels.

So-called primary dementia of psychopathic origin.

Psychopathic sleeping states after sub-manincal and maniacal waking states.

Melancholia cum stupore.

Loss of consciousness in *petit mal*.

Psychopathic paroxysmal coma states of various durations. The sleeping and unconscious states after epilepsy. Psychopathic sleeping states of the katatonic syndrome and after maniacal exhibitions.

The passive, melancholic or psychopathic sleeping periods of cyclic insanities.

The active maniacal or psychopathic waking periods of cyclic insanities.

NEUROPATHIC COMA—MELANCHOLIA.

Coma accompanying the general somatic diseases. Toxic coma of the acute infectious diseases and accompanying the action of the several classes of pathogenic poisons (diabetic, uræmic, alcoholic, febrile, coma, &c.)

Various degrees of toxic coma qualitative and quantitative up to ..... stupor ..... and heboetude according to the stationary level or rise of the cytolytic process. Forms of melancholia cum stupore which have passed from the psychopathic or function levels to the organic or neuropathic levels. The same to be said of various forms of melancholia, the depressed stadium of the katatonic syndrome and primary dementia of psychopathic origin.

Neuropathic sleeping states due to loss of function of neuron from cytolysis. Various forms of cytolytic motor and sensory paralysis.

After rating delirium and coma of toxic diseases.

CYTOCLASTIC PARALYSIS, SENSORY AND MOTOR.

Permanent paralysis—loss of function of neuron from destructive lesions of nervous system due to 1. Cytoclastic termination of acute parenchymatous degeneration of the neuron. 2. Chronic parenchymatous degeneration of neuron. 3. Cytoclasis of neuron in acute diffuse inflammation. 4. Chronic diffuse inflammation. 5. In acute exudative inflammation. 6. In softening abscess, new growths and other destructive lesions of neuron.

*Also progressive dissolution of memory descending from psychopathic to neuropathic levels. Senile loss of memory.

†Hyperæsthesia, hyperalgesia, akinesia algeria, hallucinations, etc.

‡Psychopathic monoplegias, hemiplegias, paraplegias, astasia-abasia, psychopathic motor and sensory aphasias, psychopathic forms of chorea, catalepsy.

§See Sidis "Psychology of Suggestion," Ch XXIII.

‖Unduly responsive condition to stimuli which are normally relegated to the sub-conscious. Deeper and deeper splitting of the upper controlling consciousness from the lower reflex consciousness, deeper and deeper disaggregation or retraction of the upper inhibiting constellations of neurons letting loose the energy of the lower clusters of neurons concerned with the sub-conscious functions of the nervous system. Progressive impairment of the

¶Increasing degrees of preceding or the same occurring more acutely as regards time of onset. Psychopathic melancholia agitata.

**Like many other of these psychopathic the epileptic occupy an intermediary place between the catalytic and cytolytic expenditures of energy, a psychopathic state passing over into a neuropathic condition. They begin in the former and tend to pass over into the latter. The symptoms are phenomena of both catalysis

***See Sidis "Psychology of Suggestion," Ch XXIII.

PSYCHOMOTOR MANIFESTATIONS (SYMPTOMATOLOGY).

THE CORRELATION OF SCIENCES IN THE INVESTIGATION OF NERVOUS AND MENTAL DISEASES.*

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> "No one can have a firm grasp of any science if, by confining himself to it, he shuts out the light of analogy, and deprives himself of that peculiar aid which is derived from a commanding survey of the co-ordination and interdependence of things and of the relation they bear to each other. He may, no doubt, work at the details of his subject; he may be useful in adding to its facts; he will never be able to enlarge its philosophy. For, the philosophy of every department depends on its connection with other departments, and must therefore be sought at their points of contact. It must be looked for in the place where they touch and coalesce; it lies not in the centre of each science, but on the confines and margin."—*Buckle's Essay on Mill.*

PART I.

PSYCHIATRY, ITS GROWTH AND METHODS.

Chapter I.

THE HISTORY OF PSYCHIATRY.

The history of the insane has been written again and again, and is familiar to all who deal with this unfortunate and dependent class; still a glance at this growth and progress of psychiatric work gives such graphic and incontestible evidence of the absolute dependence of the progress of the treatment of the insane upon science,

* This paper is in substance a report presenting the purpose of the Pathological Institute of the New York State Hospitals to the State Commission in Lunacy for transmission to the legislature. From its nature it had to be written in an untechnical form. As this paper not only endeavors to forecast the work of the State Hospitals and the Institute but also covers the scope of their official publications, it may not be inappropriate to publish this text in the ARCHIVES, with such modifications as have been found indispensable.

that I may ask for indulgence in once more tracing the outlines of this chronicle.

In the early Egyptian, Babylonian, Assyrian and Biblical periods, the whole subject of insanity was entirely wrapt up in the grossest superstition and relegated to the influence of good or evil spirits. The ancient Egyptian understood well enough what every other civilized nation has found out by observation, namely, the enormously destructive effects of alcohol upon the human brain. An ancient papyrus exhorting a drunkard to forsake the tavern, states "that if beer gets into a man, it overcomes the mind."

Biblical illustrations of insanity are too familiar to need mention. The insanity of Saul, Nebuchadnezzar, and the feigned insanity of King David are household knowledge. The healing of the lunatic in the New Testament describes the classical symptoms of epilepsy, and the deportment of the swine after being pervaded by the devils or unclean spirits, cast out of the Gergesene madman, gives a graphic illustration of the objective character and individuality of demoniacal possession in insanity.

A glance at the status of insanity among the Greeks is very interesting. The Hellenic world regarded insanity as a visitation of the Gods. This was natural and in harmony with the elaborate character of their mythology. Homer tells how the anger of the Gods reduced Bellerophon to melancholia and Sophocles describes the furious and destructive mania of Ajax terminating in melancholia. Euripides gives such a fine description of the cardinal symptoms of an attack of homicidal fury with epilepsy that it might well pass as the description of a well informed modern psychiatrist.

The first protest against the superstition and ignorance

in which this subject was enveloped is found in the writings of Hippocrates. Hippocrates was wonderfully in advance of his times. Here was a physician and a man of scientific knowledge, practising in the fifth century before Christ, yet his bold, self-reliant opposition to superstition and ignorance always kindles new admiration. He wastes no words in battering down the makeshift of ascribing misunderstood things to the Divinity, the invariable refuge of the ignorant.

In speaking of epilepsy the "Sacred Disease," he says: "The sacred disease appears to me no wise more Divine nor more sacred than other diseases; but has a natural cause from which it originates like other affections. Men regard its nature and cause as Divine from ignorance and wonder, because it is not at all like other diseases." He also brings out the inconsistency of singling out epilepsy as the sacred disease since so many kindred affections of the brain of equally mysterious origin ought equally well be called Divine or sacred diseases. He remarks again: "They who first referred this disease to the gods appear to me to have been just such persons as the conjurors, purificators, mountebanks and charlatans now are. * * * Such persons, then, using the Divinity as a pretext, and screen for their own inability to afford any assistance, have given out that the disease is sacred, adding suitable reasons for the opinion, and they have instituted a mode of treatment which is safe for themselves, namely, by applying purifications and incantations and enforcing abstinence from baths and many articles of food, which are unwholesome to men in disease. * * * *This disease is formed from those things which enter into and go out of the body* and it is not more difficult to understand and cure than the others, neither is it more Divine than other diseases.

* * * "Men ought to know that from nothing else but the brain (the soul and with it physic manifestations was located in the stomach by one eminent physician of the middle ages) come joy, despondency and lamentation * * * and by the same organ we become *mad* and *delirious.*" These are fine, blunt, common sense words from a scientific man, and it is a pity that they remained unheeded for two thousand years.

Hippocrates' hint as to the causal agency of epilepsy in the italicised sentence is particularly interesting, for even to-day we have only begun to search out whether epileptic attacks may not be due to the action on the brain of some poison which escapes from the intestines into the blood in course of disordered digestion. Hippocrates clearly points out too that disease of the brain is accountable for insanity. Besides this he even classified insanity with such good sense into manias, melancholias and dementia, that in 90 per cent of the cases at the present day the self-same classification is used.

Furthermore he believed that diseases of the brain were caused by "bad humors." And if the term "bad humors" be translated as poisons or toxic agents it is the scientific language which we have just begun to employ in explaining the cause of many forms of insanity.

This remarkable man went even further. He proposed *treatment* and *cure* of the insane, by ridding and purging the body of these brain disturbing humors.

The next champion of enlightenment with regard to the insane, appears in Asclepiades, about 100 B. C. He protested against poisoning patients with opium and hyoscyamus, but tried to "induce sleep by gentle friction." He would not tolerate venesection, nor dark cells, but brought his patients out into the light and gave them an

efficient diet which although somewhat abstemious was systematic and regular.

The renowned Celsus living somewhat later is rather disappointing in his treatment of the insane, for what good there was in his moral treatment, was overbalanced by the abuse of the insane, making them "capitulate," by starving, binding in chains and in beating them. His influence in subsequent periods was also pernicious, for as Tuke remarks: "It is melancholy to reflect that many centuries afterwards, all that was bad in his system was faithfully copied and even intensified, while what was good (the music, the sports, and the excitement of cheerful hopes) was overlooked; as was also the employment of friction—in other words, massage and regular exercise after food."

Of all names illustrious in the rescue of the insane from Hippocrates down to the times of men of Pinel's stamp, that of Caelius Aurelianus stands alone and unrivalled. The isolated brilliancy of this man is due to scientific knowledge and the attributes of courage of convictions, common sense and humanity. Moreover, all this in the man was happily joined with a faculty of practical application in the salvation of the insane. I can do no better than to quote from Dr. Tuke as to what this man accomplished:

"He had no patience with those who reduced a violent patient to obedience by flagellation which he speaks of as applied to the face and head, and so causing swellings and sores. He recognized the mental pain from which the unfortunate would suffer on returning to consciousness. He placed the maniac in a room, moderately light and warm and excluded everything of an exciting character. His bed was to be firm, properly fixed to the floor, and

situated so that the patient would not be disturbed by seeing persons enter the room. Straw, soft and well beaten, but not broken, was to be used for the bed, and if the patient tried to injure himself, he was to be padded on the neck and chest with soft wool."

"Minute and praiseworthy were the rules laid down by the enlightened physician, as to the duties of *attendants* and it would not disgrace, says Dr. Tuke, the corresponding regulations in the hand-book prepared by the Scotch branch of the Medico-Psychological Association. Thus they were to beware of appearing to confirm the patient's delusions and so deepen his malady. They were to take care not to exasperate him by needless opposition and they were to endeavor to correct his delusions at one time by indulging condescension and at another by insinuations. Fomentations by means of warm sponges were to be applied over the eyelids in order to relax them, and at the same time to exert a beneficial influence on the membranes of the brain."

"Restlessness and sleeplessness were to be relieved by carrying the patient about on a litter. During convalescence theatrical entertainments were to be given. * * * Riding, walking and the exertion of the voice were recommended. For the poorer patients, *farming* was to be encouraged if they were agriculturists, while if sailors they were to be allowed to go on the water. He denounced the abstinence which Celsus had extolled and asserted that a low diet was more calculated to cause than to cure madness. Further he protested in the strongest manner against putting patients in chains and trusted to the care and control exercised by attendants. He speaks against the practice pursued by some of making patients intoxicated, inasmuch as insanity was often caused by

drink. He was opposed to venesection (but not to cupping) and to reducing the strength of the patient by the administration of hellebore and aloes, on the contrary, he favored soothing and invigorating the patient by emollient or astringent application."

The work of this man does not need much comment. It speaks for itself. He is the Pinel of ancient times—a firm indomitable humane apostle of science, striking off the manacles of the insane, neglecting the twaddle of superstition and instituting measures for treatment and cure. In short, he took the insane out of the dungeons, bedlams and infernos, and placed them in hospitals, where they belong like other human beings afflicted with diseases of other organs than the brain. All this we in the light of modern times have only brought into general use within the last twenty or fifty years. The man was some seventeen hundred years in advance of his times.

Thus we find that even in ancient times science rescued the insane from the hades of superstition and reached its climax in caring for and treating them in the enlightened hospital of Aurelianus, the forerunner of the great modern hospitals of the present day in our own State. This took some four hundred years from the times of Hippocrates to Aurelianus (first century A. D.) The remarkable thing in this epoch of progress in psychiatry, is the fact that it was accomplished by three or four great leading men not even operating consecutively much less collectively, and in the face of a mythology which firmly pervaded almost all walks of life. When a man like Hippocrates starts a movement of such magnitude some one must stand at hand to take up his mantle and push the work with unflagging zeal. A great man cannot accomplish grand innovations without having great successors.

From the decay of ancient civilization to our own times the history of the insane has but repeated itself. In the middle ages common sense and science were dethroned by ignorance. Rationalism went to pieces and even the fragments fell down and vanished in the abyss of superstition. In such a benighted environment science could not thrive and all that had been done for the insane was completely lost. The insane fell into the clutches of superstition and mysticism and literally and figuratively sank into the hands of the devil, whence they were plucked forth by science centuries later through the Pinels, Tukes, Chiarugis, Daquins and ultimately placed in enlightened hospitals through State care agency and the labors of Esquirol, Foville, Guislain, Tuke, Conolly, Jacobi, Ferrus, Rush, Virgilio and Pisani.

The fate of the insane in the middle ages was simply hideous. They wandered about "possessed of Devils," without home or habitation, with everyone's hand against them and no choice between the Scylla of public cursings and the Charybdis of the care of their relatives. For we well know that *private* care of the insane, as it is liable to be in all times, is a species of private hell.

Things even came to a worse pass than this, the insane were not even accorded the saving grace of being considered human beings. They were not at times even taken to be men possessed by devils and fiends, but were held to be a different species, a set of animals or positive incarnations of devils taking on human guise. The atrocities which such a belief would entail upon the insane are hard to describe.

It is needless to dwell upon these things were it not to show that we cannot possibly expect progress in the care of the insane without fostering the scientific study of insanity.

Truly nothing was spared the insane from the brutality of the jailers armed with sticks and dogs, and the spittings and mockings of the multitude "for whom the sight of the misery of the insane became an object of amusement and recreation," up to the administration of noisome decoctions, rivaling the witches broth in Macbeth. One of these was Venice treacle, which started in with the flesh and broth of vipers, and then passing through sixty-two other ingredients, including all manner of disreputable weeds and filthy roots, strove for final absolution by tapering off with Canary wine and honey.

One redeeming feature of gentleness of humanity is the care of the insane of this age by the monks. While the monks could never free their minds from the belief that the insane were possessed by devils and fiends, compassion dwelt in their hearts, and their "*Exorciso te*" and "*Vade retro Satanus*," after New Testament teachings, were more kindly exorcisms of the devil than flails, stones, bludgeons and stakes. Churches and Holy wells accordingly often furnished a refuge for the insane.

Let us drop the curtain upon the times when the *quasi* religious man hardened his ignorance into contempt and vindictiveness at the sight of a Kepler explaining the pathways of the planets, of a Galileo elucidating the laws of mechanics, or of a Pinel smiting off the gyves of the insane. His enmity has long since smouldered into ashes, and out of them have arisen the beneficent hospitals of our own times; for meanwhile science had been slowly resurrecting

* Most undoubtedly the insane contributed the majority of victims to this evil torture. The vaporings and incredible feats which the paretic proclaims and the systematized delusions in certain other forms of insanity must have furnished abundant ease of conscience for the bigots of such times to torment lunatics as witches or devils. The doings of religious maniacs and melancholics must also have furnished sufficient blasphemy to merit torture and death We can hardly believe, however, that it made much difference with the insane, whether they were called witches or "lunaticks."

from the tomb of the dark ages, and had chosen men of Philip Pinel's stamp as her apostles to deliver the insane out of bondage. No one with even a most languid interest in the terrible history of the insane or in their present welfare, can fail to be interested in the character and doings of Pinel.

The story of Pinel has often been told, but I trust that the moral I have in mind, in repeating a sketch the history of the insane, will not stand out any the less boldly by rendering the account again.

Pinel's work, unlike that of Hippocrates and Aurelianus, was enduring because he had the good fortune to have a successor like Esquirol. The secret of Pinel's power lay in the fact that he was an apostle of science. He had that which few, if any, about him possessed—an elementary but scientific knowledge of insanity. Beside this, he had the energy and courage to defend his beliefs against the pseudo-scientific and social prejudice of his time. He saw that the insane did not belong to a different species, but that they were human beings afflicted with a disease of the brain; that they had to be considered as patients, and receive medical care and treatment in hospitals like other human beings afflicted with maladies elsewhere in the body. Pinel's good fortune was his inspiration by science.

Toward the close of 1793, Pinel, who was physician at the Bicêtre (the great French prison for the insane), could stand the sight of things there no longer. He went to one of the leaders of the French Revolution for authority to take the irons off the insane. "His demand was bold, for he ran the risk of attracting the distrust and suspicion of men always disposed to find everywhere plots against themselves." In fact, the suspicion immediately betrayed itself in Couthon's reply:

"Citizen I shall go to-morrow to Bicêtre to inspect it; but woe to thee if thou hidest the enemies of the people among thy lunatics."

The man kept his promise, and arrived next morning at Bicêtre to examine the insane himself in detail. He soon tired of the monotony of the pandemonium of screams and yells, and the clanking of chains echoing from the damp and filthy cells, and, turning to Pinel, said, "Look here, citizen, are thou insane thyself, that thou wilt unchain such *animals?*" "Citizen," replied Pinel, "I am convinced that these lunatics are so unmanageable only because they are robbed of air and liberty, and I dare hope much from the opposite means of treatment." "Well, do with them what thou likest, but I am afraid thou will be the victim of thy presumption."

Pinel commenced work that same day. Had he not in advance taken all precautionary measures which such a step required, such as proper provision for the freed slaves, he would have failed. In less than a week he had freed more than fifty lunatics from their manacles. "Some were exceedingly dangerous, and among them patients who had been in chains for *ten*, *twenty* and even *thirty* years.*

Pinel stayed two years at the Bicêtre, encountering plenty of the pigheaded opposition of ignorance, but he had the satisfaction of seeing his efforts crowned with success. The excitement created by bad treatment gave way to quietness and improvement in the patients, and tractability replaced tumult and disorder. Everywhere he went, light, air and decent food came. Promenades and workshops arose to divert into wholesome trends the

* Dr. Pargeter in 1792 says that the festerings of these manacles and cords at times actually destroyed the flesh of the extremities. In one case where the jailer had tied the patient's legs with cords, when removed, these had so lacerated the integuments, tendons and ligaments, that gangrene took place.

disordered energy of the insane. Jailers were forced to discard their sticks and dogs and had to become attendants. In short, Pinel forecast the modern hospital for the insane.

Pinel then went to work at the Salpâtrière, another large prison for the insane at Paris. Again he met with blind, malignant opposition, but achieved success in the end.

Seldom, if ever, do strokes like Pinel's make their force felt as soon as it would be expected. *Vox populi* is often not *vox Dei*, but *vox ignorantiæ*. For the people are ignorant, and ignorance fights desperately against knowledge and science.

Without detracting from Pinel's glory it would be unfair to overlook the work in Germany, England and Italy. In Germany, in several places, Pinel's work had already been accomplished. As early as 1773, no lunatic was allowed admittance to the asylum at Berlin without a medical certificate. In 1785, at Frankfort-on-the-Main, a hospital of the enlightened type existed, and also at Lubeck (1788), and at Brunswick (1793). Berlin started one in 1784.

The reason for this advance in the care of the insane by Germany is not hard to find. The Germans foster scientific research; they have found out that it pays. Science is substantially encouraged by the government, and economy, strength, prestige and humanity are the returns. Amid such a splendid galaxy of names as Gall, Spurzheim, Haller, Burdach, Reil, Oken, Jacobi and Nasse it could not be otherwise. Observe, too, how, at the beginning of the century, Germany was taking means to sow broadcast a general knowledge of insanity, that it might not be immured or become narrowed within the asylum walls. We

find that domiciles for the insane were built near the universities, where scientific investigation of the insane might be broadened out and an understanding of insanity brought to the general practitioner by teaching the medical student.

Dr. P. M. Wise, the president of our State Commission in Lunacy, has, in his recent address before the New York State Medical Society, struck the keynote of this same appeal to have a wider appreciation and teaching of insanity in our own country, especially when, in these days, we are stepping across the threshold of a new epoch in scientific investigation of insanity which bids fair to make a revolution in the progress of psychiatry.

Note, too, Germany's foremost attitude in arousing and keeping alive interest in mental science in her journals even at the beginning of this century. The magazine for Psychotherapeutics was started in 1805 and rehabilitated in 1808, with less pedagogy and metaphysic and more natural philosophy. A little later Nasse started a second journal which owed much to Jacobi, the Nestor of the German alienists who exercised a personal influence on the development of mental science in Germany.* In 1819 another journal devoted to the interests of the insane, appeared. In 1838 still another, and in 1844 Allegemenie Zeitschrift für Psychiatrie, which still continues.

Here are five journals devoted to the interests of insanity within the first half century. No other nation has a record like this. The influence of these journals on the progress of insanity has indeed been great.

* Homage is again to be rendered to Samuel Tuke, for his example influenced Jacobi who translated into German in 1822 Tuke's "Description of the (York) Retreat containing an account of its Origin and Progress, the Modes of Treatment and a Statement of Cases." (1813).

Germany's* example, then, is a fine monument for my plea of a state support of scientific investigation of the insane.

Italy was but little in the vanguard of Germany at the close of the last century. Chiarugi and Daquin had commenced reforming the asylum at Florence on Pinel's plans before the latter had begun his work.

In England, the work was taken up and continued by the Tukes at Bethlem and York retreat.

In the United States, the insane were at first subjected to the same abuses as elsewhere. But in spite of its early hardships and poverty, this country centering its efforts at Philadelphia managed not to be behind in the progress of humanitarian treatment of the insane.

As early as 1751, Dr. Thomas Bond put forth his efforts, seconded by Benjamin Franklin, for the establishment of an hospital for the relief of the sick poor and "for the reception and cure of lunatics." This hospital, too, recognized that insanity was a disease and that its victims were to be cared for and treated by physicians. It was in this hospital that Dr. Benjamin Rush gathered for twenty-nine years his experience that led him to suspect that much insanity arose from poisoning of the brain by the acute bodily diseases, an important point of view that has now come to the surface. It also should be remembered that the United States very early recognized the maxim of

* While Germany was in advance with a few institutions it is of course not to be understood that the length and breadth of the land was up to the same standard. This was the case in every other country struggling for the weal of the insane. One or two institutions were well in advance, but elsewhere they were sadly behind. In England, Tuke had enlightened Bethlem and York retreat, in Italy Chiarugi and Daquin did the same at the Florentine Asylum. In France, as we have seen, Pinel corrected Bicêtre and Salpêtrière. Throughout these countries the example was taken up very slowly. By her teachings, her journals, her hospitals, and the requirement of medical certificates, Germany had the lead.

Horace Mann that the dependent insane are wards of the State, a conception which led to their final redemption from abuse.

Twenty-four years passed by before Pinel's work advanced a single step. For Esquirol, his disciple, making an inquiry into the condition of the insane and their establishment in 1819, had occasion to write such bitter words as these:

"These unfortunate people are treated worse than criminals, and are reduced to a condition worse than that of animals. I have seen them naked, covered with rags and having only straw to protect themselves against the cold moisture and the hard stones they lie upon; deprived of air, of water to quench their thirst and of all the necessaries of life; given up to mere gaolers and left to their brutal surveillance. I have seen them in their narrow and filthy cells without light and air, fastened with chains in these dens in which one would not keep wild beasts. * * * This I have seen in France, and the insane are everywhere in Europe treated in the same way."

The second epoch in the progress of the insane is the period of passive indifference on the part of society. In several countries, in one or two institutions, the insane were released from the bondage of chains and on their way toward decent and humane treatment. But from the release of manacles to care and treatment in the hospital was a long stride, and unhappily a period of forty years from the beginning of the century awaited the insane in a second epoch of the indifference of society.* Very slowly indeed did Pinel's redemption make itself felt.

*In 1804 the law classed the insane with animals; thus the code Napoleon (Belgium, 1804) punished those who allowed "the insane and mad animals to run about free."

The insane were simply freed from their chains and nothing more. To any further progress society was indifferent. The insane were simply put out of the way, no longer actively tortured in the majority of instances, but merely gotten rid of. This was a period of sequestration, a negative mercy to the insane on the part of society, compared with previous times. After society had stowed the insane out of the way, where they could do no harm nor be heard from, this was the end of them. No one took the trouble to know whether justice and individual liberties were travestied, nor was there any pretense of medical supervision and treatment.

Accordingly the insane were stowed away in the iniquities of the almshouses, workhouses, and other rookeries, or confined with prisoners in jails. This was the epoch of social indifference, which occurred between Pinel's and Esquirol's times and the State care, culminating in the modern hospitals. This was the day of Bedlams, Pandemoniums and Madhouses, and over their doors might as well have been written the motto: "Who enters here leaves hope behind." This was not much of an improvement over the Infernos which Pinel found.

This kind of thing continued longer than we should expect. In Belgium, for instance, Guislain found it evil enough to suit the most pessimistic views of human nature. The physicians in the asylums held subordinate positions, under lay superintendents who were speculators, working the lucrative side of the thing. It must have been a fine thing to filch political money out of such poor devils as lunatics, and have their cost *per capita* reduced to seventy centimes a day. Most of the patients were under the care of their relatives, who were generally ready to believe anything of them, and treated

them accordingly. Others fell into the clutches of mercenary Judases who bid against each other for the lowest prices. The patients were shut up in cellars, or small cells, with hardly enough to eat or drink, with chains and iron rings on their hands and feet, without the faintest pretense of medical authorization. Some, when brought out of these ratholes, arrived at the asylums in a dying condition. These iniquities were still going on in a civilized country in the years of the Christian era 1841 to 1850!

This condition of things should warn the custodians of the insane not to fall back into ancient practices of barbarism, by intrusting the insane, who are really diseased and have to be treated methodically and scientifically, like all other patients in hospitals, into the hands of the laity who are ignorant of medical science. Such a condition of things would tend toward a reversion to the old system of making the insane prisoners or slaves to people who would grind out of them whatever profit they could.

When the insane have recovered from their mental disorder, but not sufficiently to be able to stand the wear and tear on nervous energy in resuming the struggle for existence, it is most important to provide an intermediate stage of *after care* between their release from the hospital and their return to the activities of life. The plan of allowing the laity to have care of the insane except in the judicious *provision for after care* is opposed to the whole course of science which has taught us that *insanity is a disease and must be treated by physicians of special scientific training.*

The history of the succeeding epoch in the progress of the insane, is too familiar to need mention. Ferrus has much of the credit in initiating this most important step of State care of the insane in France during the latter

portion of the first half of this century. Other countries independently took up the same work.

Within the last twenty or thirty years, with State care as the haven, and science as the beacon light, the insane have been guided into the refuge of enlightened care and treatment. They have been taken from the almshouse, the madhouse and pandemonium, from amongst criminals, and placed in enlightened hospitals. Dante's motto has faded from the doorway, and the hope of treatment and recovery is held out to them.

In our own State, we have good reason to be proud that our institutions are not in any way behind those of any other place in the world. The name of asylum redolent with so many hateful memories of the past has been erased and the word "hospital" symbolizing humanity and hope substituted.

The last word of the history of the insane in our own country cannot be written without paying tribute to the members of the first Commission in Lunacy of the State of New York, especially to its President, Dr. Carlos F. MacDonald, to the present Commission, as well as the superintendents of the State hospitals. The present progress in the treatment and welfare of the insane in our State is their achievement.

The history of the insane may be divided into four periods:

I. The Period of Revenge.
II. The Period of Indifference.
III. The Period of Humanitarian and Empirical Treatment.
IV. The Period of Scientific Study, Rational Treatment and Preventive Medicine.

The *first* period presents the spectacle of society under

the ban of ignorance, revenging itself upon the insane. This lasted some seventeen hundred years or more up to the times of Pinel.

The *second* shows the passive, indifferent attitude of society. This was the period of mere sequestration of the insane, witnessed in the first half of this century.

The *third* presents the more inspiring sight of the active interest of society in behalf of the welfare of the insane through legislation and the founding of hospitals for beneficent care and medical treatment. The third and present epoch we may designate as the period of empirical medical treatment. In this epoch the material welfare of the insane, such as their housing, comforts, amusements, moral and physical care, have reached a high degree of excellence.

The future and *fourth* epoch in the history of insanity will be the period of *rational* medical treatment and cure, and possibly by more radical measures in public medicine for the *prevention* of the increase of insanity. This will be based upon a more thorough understanding of the cause and course of the disease in any given case. This fourth epoch, the threshold of which we are crossing at the present time, is coincident with the **establishment of centres of scientific investigation**, in conjunction with systems of caring for the insane, in public and private hospitals. Science has hardly begun the broad and detailed investigation of the causes, origin and course of insanity. All this progress up to the present time has come about by the general march of science in medicine before even any detailed attempt was made to unravel the specific problems of insanity itself. How much more then, may we expect for the future when science will begin to use its present capacity and fitness to reach the very heart of

the problem, the scientific story of the whole life history of insanity.

This new and fourth epoch in the history of the insane, launched forth by the stimulus of modern scientific investigation, will gradually point out the way and take into account the benefits of the *prevention of insanity*.

Unfortunately, the time is not yet at hand when these measures for the *prevention of insanity* can be at all extensively or successively applied. Public opinion is not yet reared up to the scientific truths as to the sources of insanity, nor of their menace to civilization and society.

In educational directions, a scientific basis for the phenomena of human nature should be taught earlier in the schools. The innate instability of the higher and self-controlling spheres of the brain and the proneness of these spheres to undergo retraction from other parts of the brain, under the influence of toxic and other pathogenic stimuli, and the concomitant phenomena of beginning insanity or degeneracy, should have an elementary and simple presentation in the school text-books on physiology. The same presentation should be made of the physical basis of heredity and the noxious effects of insufficient food supply and poisons upon the germ plasm and nerve cells. Above all, the action of alcohol upon the nerve cell should be impressed upon the minds of growing children as soon as they are able to assimilate such knowledge. The evil sources, such, for instance, as the dissemination of syphilis that lead to the worst and most intractible forms of nervous and mental diseases are here among us; we cannot overlook them; they are factors of life and the State must sooner or later face the problem of taking strong measures to counteract and mitigate them.

As already forecast by empirical experience, science,

even at this early stage in the new epoch of the scientific investigation of the insane, shows that in the case of an individual, without hereditary defects of the brain, the conditions for recovery are favorable. The probability that retraction of the arms of the nerve cell may dislocate them from their fellows, and cause corresponding dissociation of consciousness, synonymous with many phases of insanity, shows that no irreparable damage has occurred in the brain. Its mechanism is intact, but is merely, as it were, thrown out of gear. Each tiny cellular microcosm in the brain is intact, it has undergone no destruction, but a slender rift has occurred somewhere between the connection of the cells, and fields in the higher domains of consciousness are split off. There is no longer harmony, but discordance in the inter-relation of the spheres of higher consciousness.

The nerve cell itself may even undergo quite a train of organic changes without passing over into the bourne of destruction, hence the chances of recovery in a perfectly normal individual, undamaged by hereditary burdens upon his nervous system, are most hopeful. It remains for us to correct the process of retraction, which is a sign of deficient energy of the nerve cell, and the brain may be made whole again. Such a form of treatment worked out on strictly scientific grounds has actually been applied with successful results by one of our Associates at the Pathological Institute in a case of so-called double consciousness and has been based upon the principles of pure science, and premised step by step from a scientific investigation of the case lasting many months.

Science, however, cannot be expected to perform miracles in the cure of the insane. If insanity be taken in its

early stages when the brain is free from hereditary defects, much may be accomplished and the view is hopeful. But if the beginnings of insanity have passed away, and are replaced by its later stages, whether in the individual or extended through a series of generations, the time has gone by when science might direct intervention. If a nerve cell is once destroyed, the damage is irreparable. A nerve cell is ordained with its functions but once during life, and is never replaced by a new one. If one, or two generations have damaged their nervous system and the germ plasm at the same time, and have entailed a heavily mortgaged cerebral estate upon their successors, the time for restituting the mechanism to provide for the lost energy of the nervous system has passed. Hence the constant plea of the scientist to those who have jurisdiction over the insane to seize the process in its beginnings, where it is less of a burden to the State, and more amenable to recovery, than in the final stages, hence the anxiety of the scientific student of insanity to look for the time when public opinion may at least put forth some few efforts in the direction of *preventive medicine* in insanity.

Chapter II.

THE PSYCHOPATHIC HOSPITAL.

The great importance, both practical and scientific, of apprehending the early stages of insanity, is obvious. The question is as to the means for this end. It is nothing short of a misfortune and an impediment to psychiatric progress in the large cities of this country and particularly in its metropolis, that no hospitals exist for the incipient and initial stages of insanity. The establishment of such a hospital is exceedingly important. It would encourage

a better popular understanding of insanity and educate the rank and file of the populace to bring the insane earlier to the attention of the psychopathologist and psychiatrist. For the memories associated with the word asylum still linger in the popular mind. In spite of the enlightenment of the modern hospitals for the insane there is still an aversion in the lay mind toward bringing a patient to an institution for "the insane" until the case becomes serious, even dangerous. The asylum is thought of in the nature of a last resort and used under more or less compulsory circumstances. In these hospitals for initiary stages of mental diseases, placed in the midst of the great cities, many cases would be presented voluntarily and the custom of sending patients before becoming violent or mentally irresponsible would take root and grow. We should do all in our power to concentrate attention upon a wider apprehension of the beginning and acute cases of insanity. This can in the main be accomplished by educating and persuading the popular mind to the belief that in the treatment of the earliest phases of insanity lies the greatest hope of recovery, and that this hope dwindles more and more as the symptoms become more durable and persistent. The establishment of such a hospital would be a first and most valuable step toward the fulfillment of this educational influence of the importance of sending insanity in earlier stages than is presented to the ordinary hospitals for the insane. It follows likewise that the operation of such a hospital is an important factor in bearing on the *prevention of insanity*.

Dr. Peterson's name for this greatly needed institution —The Psychopathic Hospital—embodies its functions admirably. The name psychopathic hospital would

sooner or later convey to the minds of the people a feeling different from that of the asylum. For in the commitment to the asylum, people believe that their relatives or friends are liable to be placed side by side, or at least in the same atmosphere, with the inveterate and doomed cases of insanity. This feeling certainly enlists sympathy. From this general repugnance to the asylum, and from the fact that the patients are put in a hospital for "the insane," thus branding them with the stigma of "insanity," naturally makes the family put off the evil hour of the diagnosis of insanity. The patient is retained at home, all hope is lost or the case becomes unmanageable. The psychopathic hospital in the metropolis would, in the course of time, largely do away with the prejudice that now holds back the early and favorable cases from proper treatment and study.

The meaning of insanity in the popular mind is most often crushing and conveys an element of hopelessness. If then these associations of the name are in a certain measure obstacles to psychiatric progress, we must take into account the popular feeling, especially as there are good scientific grounds for it and indulge it in a different and more hopeful conception of the early stages of mental disease. Let us substitute for the sweeping term "insanity" some equivalent, such as "psychopathy," which will convey to the lay understanding that the patients for this hospital are not yet insane in the popular sense, but are subject to a process, which if taken in hand, will prevent development into insanity. The sphere of the hospital is to seize the active percursor of insanity as well as the early stages of mental disease. The psychopathic hospital is for the reception of many patients which would not be ordinarily regarded as ready

for commitment to the asylum. Yet from this very standpoint how valuable is its sphere in prevention and cure of insanity? *The psychopathic hospital is for the reception and wider identification of earlier, functional and more curable phases of mental diseases.* According to the idea based upon the principle of neuron energy as a law governing the progression of the phases of mental diseases* the insane fall into two great classes as regards hospital treatment and care. Broadly considered the first class would comprise those early phases of mental diseases corresponding to the *functional* mental maladies or *psychopathies*† should pass into the psychopathic hospital. The *second* class constituting the organic strata of mental disease or the neuropathies‡ and belong to the hospitals for the insane. This second class is composed of two groups. The first includes the cases whose symptoms correspond to degenerative and regenerative energy cycles of the neuron, while the second includes those cases manifesting symptoms of progressive degeneration and attended with destructive changes in the neuron. These two groups should be individualized in the hospitals for the insane.

The cases of the first class are amenable to recovery. Of the second class, the condition of the first group is less hopeful though recovery is not impossible; while the condition of the second group is hopeless.

The psychopathic hospital is practicable in the large cities. This distribution of insanity relative to treatment and care based upon the theory of neuron energy cannot be carried out in practice with fixed and absolute boundaries

* Vide "Neuron Energy and its Psychomotor Manifestations." ARCHIVES, Vol. I, No. I.

† The psychopathies exhibit phenomena concomitant with dissociation and aggregation of the neurons. Loc. cit.

‡ Loc. cit.

of the divisions. While the province of the psychopathic hospital includes the functional strata of mental and also certain nervous diseases, it should also provide for the cases entering the threshold* of the upper strata of neuropathic mental diseases. Certainly one great factor of practical importance independent of the advantages of such distribution for scientific study, is that the division brings the matter of expectancy of cure to the surface.

When one reflects upon the importance of studying and treating the earlier phases of insanity and its tendency toward preventive medicine in mental diseases, it seems really strange that the evolution of the psychopathic hospital in the large cities of this country has not been anticipated. The practical benefits of the psychopathic hospital are too obvious. The fact that the plan would bestow cure upon many patients who, left to themselves or their friends, would otherwise be committed to the asylum later in a much less curable, even in a hopeless condition, answers the argument of gain over cost and the practical utility of the hospital.

Abroad, particularly in Germany, almost every city and university town operates a plan of this kind in the institutions known as psychiatric clinics. In New York City it must be said to our disparagement that the only substitute—and perceiving the great purpose of such provision for psychopathies it is more a makeshift than substitute—is a pavilion at one of the public hospitals. Facilities for study at this place are few; here the cases are merely distributed to the various large asylums in the vicinity. As this pavilion is merely a centre of distribution it has neither theoretical nor practical therapeutic value. Whether or no such an institution should be

* Loc. cit.

undertaken wholly or partly by the State is a question out of my province, but the expansion of this pavilion into a psychopathic hospital is an imperative necessity.

From the practical issues let us turn to the value of such a hospital for scientific research in psychiatry. This may be summed up in saying that the very heart of the greatest problems in mental disease lies in the investigation of the cases entering the psychopathic hospital. The impetus to progress in psychiatric research from the scientific investigation of the cases in such a hospital cannot be overrated. Many who are providing the opportunity for the growth of scientific centres in connection with hospitals for the insane or whole systems of these hospitals are prone to think that the cases for investigation lie exclusively in the sphere of the asylum. This is a mistake. *Quantitatively the material for investigation in the asylum is indeed great, but qualitatively regarded the opportunities are few.* In the hospitals for the insane the majority of the cases are in too late a phase of the morbid mental process to be suitable for investigation. A single properly selected case in the psychopathic hospital where the morbid process and concomitant psychomotor phenomena are in an initial stage of development is worth more by far for investigation than hundreds of the average run of asylum cases. The investigation of such cases may furnish the key to great laws and principles governing the whole course of mental and nervous diseases.

The first thing in inaugurating scientific centres of psychiatric research is to find their sphere of investigation. This lies largely in the study of a class of cases which could be induced to enter the psychopathic hospital.

For the sake of illustration I venture to allude to the

scientific centre of the New York State lunacy system. This institution, while in intimate touch with the hospitals for the insane, is not incorporated with one of them for the express purpose of affording extensive scope of investigation. It is situated in the metropolis to seek material for the study in one of its most important departments—that of psychology and psychopathology. But without any systematic hospital provision for the psychopathies where to individualize and collect them, our opportunities for investigation in this most important province are limited and dictated by chance and accident. The study of these cases is not taken up by the university psychological laboratories for here investigation turns in the rut of routine scholasticism and is so immersed in the study of the psychomotor phenomena of the normal individual, the college student, that the great value of making progress in the knowledge of the normal phenomena by correlative research of the abnormal is unfortunately altogether neglected. The general practitioner sees many of these psychopathies. To him they are most often a sort of *noli me tangere* to be passed on to the specialist. From the psychiatrist they receive scant attention and ultimately fall into the hands of the neurologist who so little comprehends their nature and cause, but is ashamed to confess it.

Both the psychiatrist and neurologist have practically confessed inability to cope with these cases by merely identifying the phenomena in clinical groupings under purely descriptive names. As for the meaning of the psychopathic phenomena and the underlying morbid process they have caught but little more than a glimpse.

The ideal home of centres of psychiatric research is in the psychopathic hospital and clinic in the large cities

where opportunities are also best afforded for the remainder of the diversified investigation of the institution. The psychopathic hospital would also exert a valuable influence upon the aim of such a centre of psychiatric research of bridging over the unfortunate gap in the scientific study between mental and nervous diseases.

The psychopathic hospital should include on the staff the general practitioner as well as the specialist, the psychopathologist, neurologist and psychiatrist; it should be the valuable meeting ground of both of these provinces or rather both departments of the same province. Under the influence of such a hospital an effort might also arise to seek out these cases instead of leaving the initiative of admission and committal of psychopathies and insanities to such an incompetent judge as the laity.

Stumbling blocks to the art and exiles from the science of medicine the psychopathies have been sadly neglected. Yet these same cases contain the greatest measure of knowledge for psychiatry, psychology, psychopathology, neurology and the science of medicine in general. The importance of collecting these cases in a psychopathic hospital and clinic for a wider, more accessible field of research is indeed great. Instruction in the combined psychopathic hospital, clinic and centre of psychiatric research would also be an important factor in medical education.

The beneficent influence of the psychopathic hospital is finely summed up in the closing lines of Dr. Peterson's address:* "A psychopathic hospital would accomplish a great practical good. It would be a boon to the many insane now gathered daily into a pavilion at one of our

* Inaugural address to the New York Neurological Society, May, 1898. Journal of Mental and Nervous Disease, June, 1898.

hospitals merely for distribution to various asylums. In such a hospital many cases could be treated and cured, thus avoiding transfer and commitment to asylums. Medical students and special students of psychiatry would profit from the convenience of access to the psychiatric clinics and the young graduate would enter upon practice with some definite knowledge of insanity and its treatment. But the greatest value of the proposed special hospital would undoubtedly be the opportunities afforded for those aggregate studies by many specialists which are destined one day to discover the origin and cure of many of the psychoses and incidentally to unravel some of the mysteries of mind."

Chapter III.

THE ASYLUM AND SCIENCE.

Turning now to the organization of research work in psychiatry, we must emphatically point out the fact that scientific work along the old routine lines of one-sided investigation of insanity, would be nothing but a snare and delusion; it would be a loss of time and labor; it would be an utter failure, barren of actual scientific results.

The one-sided scientific investigation of insanity by the microscope alone is not liable to yield results which a comprehensive study is naturally bound to bring about. It is equally safe to say that a restricted provision for scientific work on insanity, along the beaten track, followed for the last ten or twenty years, would, in a very short time, become effete.

The general impression seems to be not only among the laity but in the medical profession at large, and even in that branch of it which deals with the insane, that all that is necessary for scientific investigation in unravelling

the life history of mental diseases, is to bring into the asylum microscopes, certain complicated machinery for cutting thin slices of brains, an assemblage of aniline dyes to stain these slices, and a goodly assortment of various sized bottles and jars for the preservation of the brains. This is a sadly mistaken notion of the way of investigating insanity. It has been done over and over again in the past twenty years at the hospitals for the insane, and the results toward advancing psychiatry were not only highly disappointing, but the plan has actually wrought harm.

Fettered by the incompetency of clinical methods of investigating the living patient, psychiatry turned for scientific light to the study of the dead through the microscope. Thus, while in the living patient were hidden great scientific truths and vast material for scientific discoveries which might have inaugurated new trains of thought and revolutionized whole departments of inquiry, the psychiatrist was unable to reap the benefits by reason of the inadequacy of his methods of investigation.

These methods are based on a wrong plan and an insufficient conception of the great comprehensiveness of the phenomena in insanity. The methods are of the clinical kind, adapted for observation at the bedside in ordinary general diseases of the body, but so utterly unfit for the study of mental symptoms that one can hardly expect to catch so much as a glimpse of the real nature of these phenomena. One may say that where inquiry by these kinds of methods leaves off a large part of true scientific research in psychiatry begins.

Thus psychiatric research is turned aside from one of its most important domains and nearly the whole burden of the work is cast upon the microscope. In this way, save to the few bolder minds, the inspiration of the whole

scientific side of psychiatry is dwarfed and bound up in the work of the microscope and its accessories. It seems strange that so noble, so comprehensive a science as psychiatry should be circumscribed to a single unaided branch of scientific research as pathological anatomy by the methods of the microscope. But it is still stranger that this unaided branch of investigation should have been in itself circumscribed to the last degree. If the microscope is used broadly and with scientific reflection; if it is co-ordinated with many other branches of science, the research is most important in psychiatry. But in psychiatric investigation it seems as if mental vision instead of expanding as the lenses grew higher, diminished its scope of field hand in hand with that of the lens. Microscopical study in psychiatry has been made synonymous with specialized pathological anatomy of the nervous system. In fact, so specialized and restricted is this study, that what is gained in accuracy and minutiæ of facts is more than outweighed by a loss of comprehension and appreciation of their value.

This study is of a topographical nature. While it renders a conscientious account of the distribution of gross terminal changes in the brain in the last and destructive stages of mental disease, the detection of the early phases and of the processes underlying the whole life history of certain classes of insanity are entirely beyond its scope. Thus the pathological processes in the great mass of mental disease are ignored. Such a study again disregards co-ordination with pathological processes in the lower parts of the nervous system concomitant with nervous diseases. Pathological anatomy of nervous diseases presenting a simpler set of conditions for research should be intimately linked with and constitute the stepping stones to appre-

hension of patho-anatomical processes in mental diseases enveloped as they are by far more difficult conditions of study. Worst of all, however, is the fact that this investigation utterly neglects any philosophical correlation of morbid processes in the nervous system with those occurring elsewhere in the body. This seemingly constitutes the "speciality" of "specialized pathological anatomy of the nervous system"—to hold aloof from the light of analogy with the operation of the great fundamental laws which govern pathological processes in the whole body uniformly. This specialized study, not only in psychiatry, but also in neurology, has come to such a pass, that the nervous system seems to be regarded as something apart from the rest of the body, as if subject to peculiar pathological processes of its own.

This is indeed a puny effort to fathom the depths of so profound a science as psychiatry. Through this specialization its field of inquiry was isolated and the range of the intellectual sphere of the science correspondingly narrowed. This extreme specialization fastened itself upon psychiatry and blighted its genius. It rebuked that boldness of conception which diversity of study alone can bestow. Science has two sides; the mechanical side of merely gathering facts and the intellectual side of evaluating the facts and discovering the laws that underlie them. The discovery of laws, principles and generalizations is the true and highest function of science and constitutes the spirit of scientific progress; whereas if attention be wholly concentrated upon the mechanical side, science comes to a standstill. Many, however, confound the mechanical with the intellectual sphere of science. They are prone to think that the mere mechanical work of gathering facts is synonymous with

the intellectual work of co-ordinating the values of the facts. This constitutes the great danger of specialization in science. This restricted plan of research fastened its view upon a single point and neglected the vast horizon of psychiatry. The little gain in new facts is really a great loss in the range of scientific thought.

In this way it has happened that psychiatry is behind all other branches of medicine both as to valuable facts and scientific theories; it even lacks speculations and hypotheses, the fertilizing germs of scientific progress. In this position many aspersions have been cast upon psychiatry. It has become a target for querulous demands for more rapid development than the organic laws of its growth would permit. It has almost become a fashion to attack psychiatry and complain that it has lagged behind all other medical studies. This criticism comes from the votaries of other departments of medicine, and among them prominently the neurologist, who immersed in his own peculiar limited and to him all important science forgets that the progress of psychiatric research is dependant upon advances in his own department. In fact the neurologist, "normal" psychologist and the "specialized" pathologist of the nervous system are the very ones to be blamed for the narrowness of the horizon in their own sciences and the supercilious air with which they regard the investigators of abnormal mental life. Well may the psychiatrist turn to these people and say: "And why beholdest thou the mote that is in thy brother's eye, but considerest not the beam that is in thine own eye?"

It seems to me that the sort of criticism coming from the neurologist, normal psychologist, specialized pathologist, etc., is shallow and even foolish. For what is the use of

elaborating that which is perfectly obvious? Surely the obvious thing in the progress of psychiatry is that being the greatest, the most difficult and comprehensive of all medico-psychological sciences it must necessarily be the last to begin its progress. The psychiatrist has quite properly ignored this sort of criticism. At times, his just resentment has been aggravated, for he knows the greatness and difficulties of his science. Baffled in wresting out its truths without being discouraged, defeat quickening his resources, he has created the science and done all that could be done towards its advances. Yet in the midst of this he must needs suffer attacks from those who labor in a mere tributary science, stepping stones to psychiatry. He has had to hear criticism from the very ones who have held psychiatry in check by not developing or correlating their departments of research sufficiently to be of service in the difficult and comprehensive domain of psychiatric research. The psychiatrist has been in the position of Haüy, the great father of modern crystallography, whose means of observation were so rude that subsequent generations of crystallographers marvelled that he could have founded the science with such imperfect methods.

Perceiving the greatness of psychiatry in the past, realizing that the present is about to unfold its grandeur, and beholding psychiatry in the future as the queen of the neuro-pathological and psychological sciences, it is far from my thoughts to share in this conventional kind of criticism. If, therefore, in this text, I have protested against the inadequacy of the present plan of psychiatric research, it must be clear that this has been done in order that I might, according to my measure, substitute a larger, broader plan of the correlation of sciences in psychiatry which must surely encourage thought, scientific power

of the imagination and engender progress. Even now the genius of psychiatry like the fabled *genie*, unloosed from the vial, is gathering into form, the haze is beginning to take on the stature of a giant among the medical sciences, and they who have carped at its growth, will be quick to render homage to its future grandeur.

While to many it may seem unnecessary to go into details respecting the inadequacy of isolated microscopic work in insanity—for the inefficiency of this present restricted method of microscopic research in psychiatry must be well recognized—nevertheless three reasons urge the discussion of the subject.

In the first place this restricted method is inadequate because it can only contribute to the mechanical side of science, it will do little more than heap up facts. *The restricted use of the microscope in psychiatry can only give microscopic results.*

In the second place, and here I think that others who are endeavoring to build up centres of psychiatric research will see the force of the argument, this restricted plan must be rooted up and its influence cast away before we can have the freedom and means to substitute the broader plan of the correlation of science in psychiatry.

In the third place, this restricted method benumbs the whole intellectual sphere of the science of psychiatry; it discourages originality and genius, the discovery of laws, principles, and deductive forecasting of effects.

Some years since in discussing the future progress of psychiatry and neurology, a distinguished psychiatrist and neurologist said to me: "We seem to have gone as far as we can. Every subject whether in neurology or psychiatry seems exhausted. There is nothing new to work at, or nothing to add to the old things. The micro-

scope fails to give any new light." If this restriction of the investigation of both mental and nervous disease to the so-called clinical methods, and to the specialized pathological anatomy of the nervous system had produced such a gloomy impression upon a man of note, what must have been its effect upon the young observer entering either of these provinces in the fullness of enthusiasm for research. Certainly the effect would be to chill scientific imagination and flatten originality and genius. The stress of the restricted conception of work would drive him into the beaten track without his stopping to reflect upon broader plans of work. He would dig out a few more facts at the extremity of this narrow avenue of investigation and probably get the belief that this was accomplishing the true aim of science.

Since that time two great and powerful methods of microscopic investigation have come into use in neurology and psychiatry. From this it might be argued that the restricted plan of this specialized microscopic work in neurology and psychiatry was right; that it merely lacked improvement in methods. It is perfectly true that these two methods (Golgi's and Nissl's) afford a startlingly wider range of facts in the nervous system than we had hitherto dreamed of. But of what use are facts unless we appreciate their value? There must be something more than the microscope and the ability to work it. There must be *mind* to put a value on the facts. And for the mental evaluation of the fact there must be diversity of scope and the light of analogy that comes from a grasp of more than one limited department of research. If the microscope became so perfect that we could see molecules in the nerve cells, its unaided work would never give us the complete insight to the phenomena of thought, either

normal or abnormal. I think the whole conception of the exclusive restriction of psychiatric or neurological research to the clinical methods and the specialized pathological anatomy of the nervous system by the microscope is wrong and inadequate.

For considerable time the thought has been growing on me as to the great importance of fields between several of the departments of neuropathological and psychiatric research. It seems to me that the investigation from these "*intermediate fields of science*" is what is most needed at present to counteract the drawbacks of specialization. Briefly stated, what is principally needed to grasp the great comprehensiveness of psychiatric research is the bridging over of psychiatry, psychology, neurology and pathological anatomy. If this union shall be accomplished in the newer science of psychopathology there will soon follow a *renaissance* in all of these branches of research. If then I have noted certain shortcomings of the asylum methods of psychiatric research, it is to measure the better the great benefit and inspiration to psychiatry that must surely follow the research conceived by a federation of sciences.

If a restricted mechanical plan of microscopic work were the right way to investigate the nature of insanity, it would be comparatively easy to write the stereotyped report of the microscopes, machinery and glassware bought, interspersed with prophecies as to what was going to be done with these things in clearing up the mystery of mental diseases. A list of autopsies by the hundred might have also been added presenting the conventional statistical arrangement as to age, race, sex, mania, melancholia, paresis and dementia, and the tabulation of the spots of softening, atrophy of convolutions, thickening

of membranes, blood vessels, etc., or other gross signs of wreckage of the brain.

The mechanical method of applying the microscope would make things go smoothly in establishing laboratories for psychiatric research since it minimizes the burden of thought and scientific reflection.

The time has not arrived, nor will it ever come, when the scientist can be replaced by the mechanician and scientific thought by machinery.

Were this the way of investigating scientific problems of insanity, we would have simply had to carry the microscope into the asylum. There would have been no need of making such frequent explanations to the visitors of the Institute, in answers to their surprise of not finding such an institution centered in one of the hospitals for the insane, and confined to the *direct* study of the objects of its research, the brains of the insane.

The impression that scientific investigation of mental diseases is shooting wide of the mark and not attaining its object unless confined to the study of the insane themselves and their brains, seems deeply rooted in the minds of not only the laity, but also of the self-contented, routine-working, unreflective pathologists and psychiatrists. It makes at first, one blush, then uneasy, and finally simply bored when one has to reiterate to many a would-be scientific specialist, the same obvious elementary reply to the puerile question: "What has this to do with insanity?" when one man is observed at a desk, patiently studying the workings of the nervous system of the cockroach; and another is seen experimenting upon a perfectly sane individual and producing artificially some interesting departure from the normal operations of the mind, or a third investigator is inducing artificially a

poison into the nervous system by an experiment on one of the lower animals; or a fourth investigator is watching the effects upon the nervous system of some ordinary disease of every-day occurrence, like typhoid fever, dropsy, or pneumonia. The time has not come, nor will it ever arrive, when any one can expect to understand normal or abnormal operations of the mind, by simply gazing through the microscope at the brains of the insane.

Fortunately this narrow conception of restricting the vast domains of psychiatric research to mechanical microscopic work has not been allowed to govern the planning of the scientific centre for the insane in the State of New York. The guardians of the State System of Lunacy have foreseen the advances that may be made by properly conducted scientific investigations of the insane, and have sanctioned the plan of departing from the beaten track.

There is but one way ever to expect success in the scientific study of the insane, and that is to conduct such investigations from a comprehensive and many-sided standpoint. This is perhaps more necessary for insanity than for any other subject that science deals with. What we want is an intelligent, methodical study of facts, phenomena, inductively collected observations and experiments, aided by the cautious but indispensable use of theory and hypothesis.

Scientific investigation of mental diseases must be unshackled from the narrow circumscribed conceptions which have so long governed it. Psychiatry must be freed from the confines of the asylum walls. The research must be broadened out and brought to bear on a great many problems which cannot be found within the asylum. The investigation must be brought forth into the outside world, and be applied to the great and varied number of

phenomena which lead up to an understanding of the *sources* and *nature* of insanity.

The difficulty with the investigation of insanity in the asylum, is this: Insanity does not develop within the hospitals, because the patients are brought there after the symptoms have developed and often gone far on the highway of mental derangement. As a rule the patient is not brought to the asylum unless his mental malady has become so well established that he has become mentally irresponsible. Now on the face of the matter, it is hardly sensible to expect that we can get an insight into the deepest problem of science—the mechanism of mind, its variation, its operation, its growth and decay, its normal and abnormal manifestations—unless we have the opportunity of studying such operations in their very birth.

The direct and exclusive study of the manifestations of the insane in connection with some one single method as studying the microscopy of the brain in the asylum is the poorest way of attempting to attain any real scientific results. Such study is always prone to become narrow, and forget the enormous comprehensiveness of the great and diversified standpoint of the various factors in the source of mental diseases. The point may be illustrated by a single example. Suppose a man born of three or four generations of alcoholic ancestors, with a hereditary deficiency of the capacity for elaborating nervous energy. He attempts to go through the wear and tear of life, with a minus sign set down against the energy of his nervous system by the abuses and profligacies of his ancestors,* and tries to make good that deficient energy, by artificial means. He drinks alcohol or uses other stimulants to supply this lack of

* Vide "Neuron Energy and its Psychomotor Manifestations."

energy. (This is the meaning of the "craving for stimulants" in many men). He increases the mortgage on his nervous system, a mortgage started by his ancestors; and the penalty is ultimate bankruptcy of the capacity of the working power of his brain. He hovers on the borderland of insanity for a time, and is finally brought to the hospital. After spending months and years in the hospital for the insane, in a futile attempt to restitute a misspent energy of his nervous system, or eking out what unbalanced energy remains there yet, he finally dies, and often enough, by some intercurrent disease. It is perhaps unnecessary to go into details to show how futile it is to trace the life history of the patient's cerebral events with their parallel psychic manifestations, when we are given only the last paragraphs of the final chapter to work out the narrative. The task is simply impossible. One may as well go blindfolded through the first nineteen miles of a twenty-mile pathway, full of detours and devious turns, and then attempt to recount its topography and windings by going through the last mile without the blind. Yet just such work is being attempted all the time, and little good does it accomplish, in adding to the store of real knowledge of the why and wherefore of insanity.

It is perfectly true, in the case just cited, that with the microscope a number of changes may be found in the brain structure. As a matter of fact, they have been set down with much precision, according to the development of the methods of microscopic investigation at the time of record. The literature of insanity contains plenty of descriptions of alterations in the brain, in old inveterate cases of insanity, where mental disease has converted the edifice of the mind into a mass of ruins. When now the question comes up, as to what these changes mean,

and the vital query as to the significance of these changes indicative of wreckage of the brain, then the same literature and the same observers remain silent. When it comes to the essence of the whole problem, the *meaning* of the changes that are seen under the microscope, the more important task of rising above the facts to their interpretation, of reflecting on the causes and course of these changes, remains almost wholly unaccomplished; in short the whole history of the psychopathological processes is sadly wanting, the very thing we wish to know. The conception and method of restricted microscopic work in psychiatry are fundamentally wrong. The most that such observations can point out is that the brain has gone to ruin, and this anyone with sound sense might well enough infer without taking time and trouble to pore into the microscope. The tremors and unsteadiness of the muscles, the unfaithful conveyance of messages from the outside world, into such a man's disordered brain, the insurgent gamut of his passions, the brutal and unbridled fury of his loosened sub-consciousness, and finally, the imbecile babblings indicative of the severance of the connections in the lowermost parts of the brain, all proclaim the ruin of the brain even to the most casual observer without using the high power lenses.

I dwelt upon this case, because in the minds of many this is the kind of material and the aspect of the problem that is to be given to the scientist to unravel some of the mysteries of insanity. In other words the selections are to be made in the asylum as to the mode and manner of carrying on scientific work. The discrimination and choice of the problems and the study by the microscope were hitherto directed by asylum men. This, at first glance, seems quite natural. The asylum physicians are

to tell the scientist what to do, and how he shall work, how to use his materials and problems. This would seem a delightfully simple solution of the whole question—for by far the most arduous work in science is not in the material but in its mental sphere. The mental side of science is the master which governs the mechanical work in the external world. The ability to attain conceptions guiding science in gathering and co-ordinating causes and effects; the operations of inductive and deductive reasoning; the ability to suspect, forecast and predict the operation of causes; the judgment in selecting the fit problems from the unfit; the guidance of investigation and observation; the fashioning of theory and speculation in the scientific use of the imagination; all these constitute the highest and true aim of science and also its most arduous sphere of work.

Unfortunately such a plan as this—the general guidance or control of laboratory investigation of psychiatry by the asylum—still prevails as a general rule. Asylum physicians are to pick out cases here and there, preserve the brains, send them to the scientific centre and have the material "worked up for publication and contributions to science." Plans of this sort may be "practical" but for the "theoretical" purposes of science they are not liable to engender and encourage progress.

If the scientist is to be under the direction and control of the asylum physicians, and is compelled to shape his investigation of the problems befitting their conception, and is to be restricted to investigation of such autopsy material as they may see fit to choose, his energy is liable to be crippled. It is easy to ask for results or plan out work for another, especially when we are more or less unacquainted with the enormous details and complications

of the physical methods for investigation, and leave in the background the mental methods of science that such work requires.

One of the positive obstacles in bringing a scientific institution for investigation of the insane in working order is to be trammeled by worthless cases and useless material. Another difficulty is to have the fact realized that nine cases out of ten, and that ninety brains out of a hundred chosen at the asylum and sent to the central institute contain insuperable difficulties for investigation, and their study most frequently contributes nothing to the advance of psychiatry. Furthermore, when such brains are sent to the scientist, the constantly changing intricacies of the problems of preservation are liable to be ignored, for these are to be learned by experience only, instead of following a stereotyped set of rules. The brains are generally spoiled by being improperly preserved; they are quite liable to have been treated by methods of preservation which render them unfit for the application of the latest and most modern methods of investigation. The time has passed when one or two routine methods were used indiscriminately for all cases of patho-anatomical investigation of the nervous system. Science is now in possession of a great number of methods in this branch of research and only years of experience can determine the adaptation of the particular method for the case.

A difficulty very liable to be encountered in establishing laboratories or institutions for scientific investigation of the insane lies in the fact that internes and other members of the staff are rather generally expected to be able to plunge into the intricacies of scientific research without any preliminary training. Naturally the results are

disappointing. For it is not sufficient to have a given theme of research planned out by the scientist, the work must also be entrusted to a man of scientific training. If scientific research is to be extended among the staffs of the hospitals at least one or two men in the hospitals should be chosen with regard to their *previous scientific training* and not merely on the basis of their capacity to do the clinical or official routine asylum work. For such work, excellent as it may be in itself, does not enable a man to carry on scientific research.

It is unfortunate for the progress of scientific investigation of insanity that psychiatric research work seems to be held so simple a matter that any one with a little training may launch forth into the successful accomplishment of investigating the pathology and psychopathology of the nervous system. If men in the hospitals are to do scientific work they should have a good, solid *foundation laid for this work by preliminary education* in their undergraduate and medical (and post graduate medical) curriculums. *A biological and psychological training* in the undergraduate courses giving a broad scope of reasoning over the facts in pathological anatomy, psycho and cytopathology is not only highly valuable but indispensable. The science of medicine should be more generally coupled with biology and psychology.

Medicine is an art, and by far the greater majority of physicians are practitioners of this art, and we must free ourselves from the popular belief of confounding the physician, the practitioner with the scientific investigator. One may be a scientist without being a physician, and one may be a physician without being a scientist.

If medical superintendents of the hospitals for the

insane desire the members of their staffs to join the work of the scientific centre, they should choose among the men one or more who have had special training in some particular line of research as, for instance, in general pathological anatomy, combined with a knowledge of normal histology of the nervous system, or in some other branch of research, such as cellular biology, physiological chemistry, psychology, psychopathology, etc. Only after these conditions are fulfilled is the extension of scientific work to the hospital staffs feasible.

With some general as well as special scientific training among the members of the staff scientific work can be extended into the hospitals most profitably. To ask the director of the laboratory and his colleagues to supply this foundation, to cast aside their own problems and give up their valuable time, the result of years of training, in teaching what should have been learned during the college curriculum, is not only to retard the development and progress of the laboratory, but to bring its activities to a standstill.

Within the past decade two methods (those of Nissl and Golgi) have been developed in the microscopic investigation of the nervous system which have been hailed with delight by the psychiatrist, as these powerful methods open up exceedingly valuable avenues of investigation in the pathological anatomy of mental diseases. It is singular, however, that the impression should gain ground among many psychiatrists that all that is now necessary for the members of hospital staffs to take advantage of this lately arrived and long delayed opportunity for advances in the difficult domain of pathoanatomical research of mental disease is to master the mere *technical details* of these methods.

To master such a method as Nissl's is a comparatively insignificant task, but to interpret the results gained by the use of the method is quite another matter. This involves a wide knowledge of cellular biology, general pathological anatomy, and, above all, of the *general dynamics* and *organization* of the nervous system.

Furthermore, it is mere mechanical work to array facts concerning changes in an individual cell or group of nerve cells in some instance of a mental malady brought to view by Nissl's or any other method. To attain the real aim of science, however, we should reflect upon the meaning of these facts, and above all endeavor to connect them with the changes in *function* of the particular cell or set of cells involved and to ascertain what part the diseased cells play in the general *organization* and *functional interrelation of various parts* of the nervous system.

Facts are the building stones of science. Many devotees of science never rise above the mediocre position of carting the stones from the quarry and dumping them in conglomerate heaps; they use their methods in a routine fashion and gather blindly and without reflection facts which are often trivial and worthless. The true scientist is like the architect; he must first realize the *purpose* and *plan* of the building; he must know the *value* of the material and *select* it with great care. The true scientists not only gather valuable facts but also worry about their interpretation and the laws which govern them.

Familiarity with the mere mechanical side of technical methods does not enable one to appreciate facts, nor does it give him a knowledge of the appropriate application of the methods.

In brief, to expect hospital men to accomplish scientific research in mental pathology with little or nothing more at

their command than familiarity with one or more methods of technical investigation by the microscope gained by a few days or weeks of study in the laboratory is as sensible as to expect a student to understand and intelligently use a foreign language by drilling into his mind a few rules of syntax. Without general and fundamental knowledge of the subjects to which scientific methods of investigation are applied, the mastery of these methods places the scientific novice in much the same position as the patients afflicted with mindblindness who see perfectly well with their eyes, but are unable to recognize the things seen.

The director of the scientific institution and his colleagues should not be called upon to overcome scientific mindblindness. This seriouly interferes with the primary object of the whole scientific work—namely, the investigation into the laws of insanity. To achieve such work, the scientific standard of hospital men must be raised. It would be advisable that examinations of candidates for positions of internes and juniors should provide for the entrance or choice of men with the requisite preliminary scientific training to make feasible the extension of scientific work into the hospitals.

If a scientist is to investigate the problems of insanity, he must be left absolutely free and untrammeled in the selection of such work which wide experience has taught him to expect good results. He must not however isolate himself, but should be in constant touch with his colleague, the hospital physician, advise and collaborate with him.

Our statement of the truth as to the relation of science to the asylum should not be taken as embodying the faintest echo toward anything derogatory to those who devote their whole lives in treating and ameliorating

through clinical studies, the welfare of the most difficult and trying subject in all medicine, the unfortunate and dependent insane. We ought, however, to acknowledge candidly that few, if any, can learn to accomplish the intricate duties of the treatment and welfare of the insane, grasp the clinical science of psychiatry, master in addition the details of other fields of scientific investigation of insanity, and keep abreast with the advances in all of the stupendous side issues which such investigation must necessarily involve. It lies beyond any one man's capacity to master two or more provinces of science in these days of specialization. Life is too short.

There are a hundred different ways of investigating insanity. How is any one who is not familiar with these methods and working with them every day, to exercise the discrimination as to which shall be used to carry out a particular kind of inquiry? The work of microscopic examination of the human nervous system at the present day, a single branch of inquiry in the scientific investigation of the insane, is a herculean task. In fact no one man working months even in a single case, can accomplish it. Such work has to be divided up among several investigators whose training in his own particular specialty embraces no short period, in order to avoid the pitfalls of error, which constanly beset the pathway of investigation.

There is no royal road to science, nor is there any single way of examining the brain. Several methods, each with all of its intricacies and variations, in most cases have to be used simultaneously. When the brain is once taken out of the body and put in one preserving fluid or another, to make it fit for the preparation of thin, almost diaphanous tiny slices, which are stained with various dyes, for microscopic study, we may induce plenty of

artificial changes in this procedure, changes that have no existence in the brain during life. All these things have to be taken into account and nothing but actual experience, learning from our failures and mistakes, can guard against the pitfalls of error.

Moreover, when an insane patient dies of some intercurrent disease, such as pneumonia, fever or some other secondary malady, having no primary relation to his insanity, the poison of the intercurrent disease leaves its traces upon the nerve cells, and greatly interferes with the determination of the pathological processes correlative with the symptoms of insanity. Such cases are at present of little, if any value, for scientific investigation. A set of lesions have been superimposed upon the pre-existing ones in the brain correlative with the symptoms of insanity, and it is hard to discriminate between the two sets of changes. All this is not liable to be taken into account by those who in their eagerness and enthusiasm for more scientific light upon the mysteries of insanity are naturally prone to select cases like these for investigation.

Even if the brain were properly preserved; cut into sections; perfectly stained in a dozen different ways, and weeks of study embodied in writing in the descriptive composition style: that the nucleus of the cell is "swollen," its body is "shrunken," "cloudy," "pigmented" or "unduly granular;" that its granules are "too fine" or "too coarse," or that its tail (neur-axon) is "thickened" or full of "holes." What of it? What good does all this do, if during the life of the patient there were no observations or experimentation upon the psychomotor manifestations beyond such ambiguous descriptions as "semi-delirious," "semi-stuporous" or "partially demented." This is like reading a book by studying minutely through a microscope the shape, size and color

of the letters without the attempt to penetrate into their combined meaning. The mere heaping up of facts without understanding them as little constitutes the function of true science as the conscientious counting of stars deserves the name of astronomy. Piles of ungeneralized and unclassified facts in science are often so much rubbish. Pathological anatomy is in need of interpretations of its masses of facts by the aid of biology, cellular biology and psychopathology. In fact, observations by the microscope form a relatively small and secondary part of psychiatric research. Its great sphere is the psychomotor manifestations themselves which little more than shadows across the microscopic field.

Cases at the hospital for the insane must be *critically selected* for study and experiment; their psychomotor manifestations closely studied by observation and experimental methods borrowed from the domain of psychology and psychopathology. Furthermore a progressive series must be found in which the definite phases of the psychomotor manifestations correspond to certain stages in the whole course of pathological process.

It is clear, then, that there are many drawbacks to the direct study of insanity in the loose and restricted way in which it is carried on at present. It is the *largest problem in science*, and it cannot be imprisoned within the asylum if we ever expect to find its solution; and the present time bids fair to justify such an expectation, provided the study of the problem be properly and broadly undertaken.

I am aware that it may sound sententious to speak in this way of the futility of the restricted method of attempting to study insanity directly within the asylum walls, but I cannot help pointing it out since it is the wrong way of solving the problem. Ninety-nine brains out of a hundred, the symptoms of which we are asked

to explain by the microscope, are at present absolutely worthless for study. It is a mere waste of time.

Why is psychiatry in the rut in which we find it to day? Because, frankly speaking, as intimated in the subsequent text devoted to psychology and psychopathology in the next section, psychiatry has no appropriate scientific methods to work with in studying its field of inquiry—the abnormal phenomena of consciousness. The only methods which psychiatry has are *clinical* methods. These are appropriate only for investigating the phenomena of the *lower parts of the nervous system* and *symptoms of the body* and are wholly incompetent to investigate the abnormal manifestations of the *higher parts* of the nervous system correlative with abnormal states of *mental* life. The investigation of the bodily symptoms in insanity are of the highest value, because through the body we may attempt to correct disorders in the nutritive supply of the brain and restitute pathological expenditures of energy of the nerve cell, but in attempting to investigate *mental symptoms* psychiatry must use the methods of pathological psychology or psychopathology.

Chapter IV.

PSYCHIATRIC INVESTIGATION.

In the last chapter we have pointed out a very natural reason for the backwardness of psychiatry after other branches of medicine have made considerable and even brilliant advances. Psychiatry has had to wait until several tributary sciences, especially the science of consciousness—psychology—attained a considerable degree of development. At present these tributary branches have reached a growth and capacity to enter the service of psychiatry and its future is indeed grand. The story

of the progress of psychiatry is simply the story of the progress of any other science. Every science, no matter how far it may be advanced, has had its infancy. So it is with psychiatry, and it would be exceedingly presumptuous to take the science to task, so to speak, because it is in an early period of growth. We must remember that this is one of the youngest departments of all medical sciences. It is only twenty or thirty, or at the outside, fifty years since psychiatry was recognized. The understanding of insanity was exceedingly late in emerging from the ignorance, prejudices and scholasticism of the middle ages.

It must be borne in mind too that the empirical development of the art of psychiatry was inevitable to herald the birth of the science. The material welfare of the insane, their recognition as wards of the State, the building of hospitals, medical care and treatment, had to be worked out empirically in their natural course, and all these experiences had to be gained as a starting point for scientific progress in insanity. The function of art is utility, that of science, ascertaining truth; the one seeks to control phenomena, the other gains foreknowledge of them. As knowledge and civilization advance, one of their greatest achievements is to replace the empirical faculty of control represented in the sphere of art by a scientific basis. In any branch of knowledge capable of practical application, art develops first and grows up to the limits of empiricism. Then science appears, replaces the empirical basis of art and continually expands and strengthens its power of control and utility by placing the predictive power of science at the service of art. Looking forward into the future, it seems to me that this is happening to psychiatry. The art of psychiatry has attained the limits of its (more or less) empirical develop-

ment; the true science of psychiatry is now beginning to appear, and from now on will bestow on the art the fertility of a scientific basis.

Psychiatry has reached the limits of the methods used for the last twenty and thirty years. It has done all that it could in that direction. Future fields of investigation are perfectly barren, unless this science gathers new facts. This it cannot do unless removed from its rut makes use of methods which at present it does not possess, and is correlated with other affiliated paths of investigation in medicine, biology and psychology.

There is a right way and a wrong way of attempting to investigate insanity. The wrong way is to restrict the whole study of insanity to the brains of insane patients, long after all clues have disappeared from scrutiny. The wrong way again is to study the brain as though it were apart from the rest of the body and subject to peculiar laws of its own in the origin and course of disease processes. Investigators in psychiatry are liable to take but little heed of the advances and investigations in morbid processes which take place in other parts of the body, such as the kidney, the lung, or even the humblest constitutents of the organism, such as the simple tissues. The process underlying disease and its several phases which we call degeneration, inflammation, hyperplasia, etc., and wrongfully intimate as distinct entities, are of the same fundamental nature in these simpler organs and tissues as in the complex nervous system. Presented under simpler conditions for investigation in the simpler tissues and organs, the light of analogy is most important for the valuation of the homologous pathological processes underlying mental and nervous diseases. But many have fallen into the great

danger of specialization in studying the pathological processes of the nervous system. For specialization coerces the attention to a single part and is prone to breed neglect of the relation of the part to other parts and to the whole. No one can expect to understand pathological processes in the nervous system by studying them in that system alone. To understand morbid processes in the nerve cell one must study them side by side with a knowledge of the cell in general, and correlate the study of the pathological anatomy of the nervous system with the general pathological and physiological laws valid for the organism as a whole. What is needed *is less* "SPECIALIZED" *and more* "GENERALIZED" *study of the pathology of the nervous system.*

If I were asked to give any one prominent reason why we have so little scientific knowledge of the life-history of insanity, I would say it is because of insufficiency of methods of investigation and its restriction, for instance, to the mere mechanical microscopical work on the brains of the insane. The enormous advances and revolutionary methods in the anatomy and physiology of the nervous system, in psychology and psychopathology, in cellular biology, and in the study of pathological processes in the body at large seem to have remained outside the pale of the asylum walls.

The psychiatrist seems to think in studying the scientific aspect of insanity, in investigating the pathoanatomical changes in the brain that he is dealing with something apart from the rest of the body, apart from every science except psychiatry and need not be concerned with general knowledge and methods which mark the enormous advances of the present day in normal and abnormal psychology or psychopathology, cellular biology,

physiological chemistry, comparative neurology, general pathological anatomy, cytopathology, etc.

It might seem as though it had been intimated here that microscopic investigation of the brains of the insane in the asylums was of no use. This is not the point. The protest is against *exclusively restricting* the investigation of insanity to such a province. The investigation of the brains of the insane in certain critically selected cases at the asylum, under the guidance from beginning to end of a life study, of the methods of this field of investigation and of a correlated study with disease processes occurring throughout the body in general is of the utmost value. The only protest has been against this constituting the whole and exclusive field of scientific investigation of the insane.

No such restricted investigation can hope to do much more than to set down a few desultory facts in the ultimate chapters of the life-history of insanity, and even then with no explanation as to what these facts mean or how they have come about. As it is now, we are quite familiar with the gross alterations that go hand in hand with wreckage of the brain in old inveterate and terminal cases of insanity, but we know comparatively little of what these changes mean, and still less as to their relation to the production of the patient's symptoms during life.

While the undue subordination of the many-sided domain of psychiatric research to microscopical work on the brain is unphilosophical and restricted, this work in itself is extremely complicated and the value of a commanding view of its intricacies has not had as general an appreciation at the asylum as might be desired. In this branch of work there are dozens of radically different plans of investigation, and each one of these with its

several technical methods and their variations and complicated details, has a specific and definite object to attain that no other method can give. It takes years of large experience with these methods of investigation to determine which one will subserve the best use; for one must plan ahead, from the very moment the brain is removed from the body, and apprehend, in a general way, the character of the disease process which is at work to choose the particular method of exposing its traces upon the nervous system. Very frequently provisions have to be made for the simultaneous use of several methods of investigation of the nervous system of any one particular individual taken at the stage of the disease which bids fair to yield interpretable results. Hence the great embarrassment which the scientist is constantly encountering in material sent to him for investigation is the fact that it is either placed in some fluid which is utterly unfit for the particular line of investigation or it presents some inappropriate phase of the pathological process.

In an institute for the scientific investigation of insanity, it is a bad plan to burden the scientist with autopsy material selected and preserved by any one who lacks the experience and training in the methods of microscopic study which alone gives discrimination as to which one of a great many methods is fit to use, and it is wrong to put the scientist to the impossible task of elucidating anything from such material. Yet, as a general rule, the rather elementary idea seems to have taken root that the operations of such a department are to be carried on by placing the scientists in its charge in the untenable position of investigating brains that are either unfit from the selection of the stage of the disease or impossible of investigation by reason of unsuitable preservation. It is

unreasonable to suppose that any one can gain knowledge of the material best adapted for profitable pathological study or the intricate technical methods of this investigation without making it a subject of detailed and specialized study.

With the exception of interpreting the results of study of abnormal changes in the brain with the microscope, the preservation of the brain and other organs of the body is the most important datum in the whole investigation. For if the first steps in the investigation, the details of preservation for microscopic study, be wrong or inefficient, the accomplishment of the subsequent steps of the research is out of the question. The scientist must have complete control of the scientific work, and yet work hand in hand with his scientific colleague, the clinician.

The sections cut from the brain for microscopic study are but one-ten-thousandth of an inch thick, but the surface covers over one hundred square inches. It would, therefore, require the study of millions of these sections, which are generally but one-half the diameter of a penny, to make the microscopic examination of the brain in any given cases of insanity at all complete. The human nervous system has such a large volume and is so extensively distributed over the whole body that much judgment must be exercised in choosing the particular regions upon which to concentrate the bulk of the microscopical study. It lies beyond the capacity of a single observer to make a complete examination of the brain. It requires a force of several men to divide up the work within limits that can be accomplished. No wonder, then, that the work at the Institute, even in this single department of microscopic study of the brain, has to be subdivided and the results correlated weeks or even months after the

investigation is started. In fact, in addition to the herculean task of examining the abnormal brain one must constantly have at hand sections from the same regions in the normal brain to measure and compare the changes in the abnormal brain.

Few realize that it takes years for an investigator of even the largest opportunities to collect material from the bodies of patients suffering with any particular form of disease, to correspond to all the phases in the pathological process of that disease. People seldom die in the great majority of diseases, until the process underlying the disease is well established, far advanced or has reached terminal, often destructive stages, so that we have no clue for tracing out the origin and course of the morbid process.

In a particular disease, for instance, we had to wait a number of years before any clue could be obtained to the origin of certain peculiar destructive canals running up and down the spinal cord. Several years after finding the terminal result, the beginning of the disease was seen, in which state patients exceedingly seldom die. But the beginning and initial stage of the disease was so different from the terminal and destructive alterations that the relation between the two was not recognized. Finally, within the past year, a patient happened to die in the middle stages of the disease, and now piecing all the stages together, we are able to record the pathological process underlying a hitherto unrecognized disease of the spinal cord. So it is with disease processes in insanity. If the brain is examined at some particular stage in the course of the disease, this does not by any manner of means tell us the whole story of the morbid process, it is a mere episode in the life history of the disease, a portion of a

single chapter, which perhaps forecasts the next, but tells us very little about the preceding chapters. We have to trace the history of the early phases as we have opportunities of finding them, beginning at the first, but certainly not at the last, and working backward, a decidedly wrong order in such an enormously complicated problem as relates to the pathology of mental and nervous diseases.

The well nigh insurmountable obstacle of the direct study of insanity within the asylum is that the most difficult aspects of the problem are encountered. In most of these asylum cases the gap between the effect and cause is too great for induction to span the bridge. Nor, as a rule, can we put the materials from the asylum under our immediate control and experiment for varying the conditions indispensable to the inductive method. In studying the earliest phases of insanity these difficulties are greatly reduced. These earlier phases are nearer to the causal end of the morbid process manifesting itself in a series of successive phenomena amenable to control and experiment. By a series of experiments in which by successively varying the surrounding circumstances and then carefully noting the facts, undesired perturbations may be eliminated and principles and laws may be discovered. This accomplished we may use the laws deductively and descend to the facts, bringing more and more of them into harmony and within the fold of the law. After this stage in the investigation—the discovery of a guiding principle—the later phases of insanity, constituting the majority of cases in the asylum, may be more clearly understood. Finally, science being in possession of the secrets of the early stages and the predisposing factors of insanity will exercise its highest power of forecasting and controlling phenomena. This being at the disposal of

psychiatry as an art, may yield practical therapeutic and prophylactic methods far exceeding our most sanguine expectations.

It is in the study of the early phases and predisposing and proximate causal factors of insanity that one begins to realize the comprehensiveness of the science of psychiatry and the enormous extent of its ramifications. It is here that the play of the correlation of many sciences comes into action.

We must proceed from the simple to the complex. The simpler aspects of the problems in insanity—simple only in constituting the scientific order of progression in the advance of psychiatry, but otherwise exceedingly difficult and comprehensive—can only be solved on the basis of a general comprehensive work. The work required for the investigation of these early phases include, for instance, the study of the architecture, cytology and functions of the normal nervous system; of pathological processes of the body in general and of the nervous system in particular under the influence of hurtful stimuli such as poisons, abnormal fatigue, diminution of food supply to the nerve cells; of the development of the brain both phylogenetically and ontogenetically. This study from the standpoint of phylogency and ontogeny is most important. For it gives an insight into the laws which govern the dissolution of the nervous system, the reverse process of evolution. *All mental and nervous diseases are manifestations either of the retrogressive process or of incomplete and defective evolution.*

We can realize now how meaningless and futile mere mechanical and microscopical work in psychiatry may become without correlative knowledge of the evolution of the nervous system and of the functional inter-relation of

its parts. Without such study microscopic work in the nervous system is blind and does not know what to do; it gropes in the dark and labors aimlessly in the hope of making some valuable discovery by sheer accident.

Generally speaking, the organization of the nervous system in relation to function may be described somewhat as follows: The most supremely organized parts of the nervous system, the last attainment in man's evolution, the most precious part of the brain, which it has taken eons of time to evolve, which gives man his discrimination, his powers of ratiocination, his self-control, are the most unstable parts of the make-up of the nervous system. These higher and last evolved parts of the brain are prone, in the presence of pathogenic stimuli, to become dissociated from the remainder of the nervous system first and with their dissociation appear the first beginnings of unsoundness of mind. It may be seen, then, how absolutely essential it is to have the complete story of the evolution of man's brain, both in the individual and in the species, and to find out how this nervous system has been progressively built up, one part added after another, corresponding with higher and higher functions.

We may watch this in the development of species or in the child's brain. When the child comes into the world it has absolutely nothing to its credit in the functions of the nervous system, except the operation of that lower part of the nervous system which presides over the most fundamental functions absolutely necessary for the maintenance of organic life, such as respiration, circulation and a few reflexes. Little by little, higher and higher portions of the nervous system develop. Slowly and progressively the sense organs transmit desultory and uncorrelated messages of the physical aspect of things

in the outside world. Still later the messages from the outside physical world are correlated in a simple and elementary form and a low grade of consciousness and recognition of things in the external world begins to dawn upon the child. Ultimately, by the use of the very highest parts of the brain which man possesses, the child learns to discriminate among these impressions and their correlations to the outside world, as to what is significant and as to what is insignificant. Still further along, as the child becomes older, by constant use and education of the supreme and highest part of the nervous system, he learns self-control and inhibition over the lower parts of the nervous system and higher and more complex forms of syntheses of consciousness.

These supreme centres of the nervous system, which exercise control and inhibition and a bridling of the lower parts of man's nervous system, which latter we share in common with the animal, are the last to ripen and mature in the education of our brains. The maintenance of this part of the nervous system requires constant vigilance and exercise all through life, and a great majority of people never completely learn to make these centres less unstable than they are bound to be through the laws of evolution. A whole lifetime does not suffice for great multitudes of people to gain sufficient stability of these centres by constant exercise and training. The consequence is that by over-fatigue, deficient nourishment, or by poisoning of the nervous system, a progressive dissociation and finally disaggregation of the nervous system occurs in the reverse order of its evolution. The highest and most complexly organized, and naturally the most unstable portions become dissociated first, as witnessed in *neurasthenia*. Then in a steady progression the dissolution

descends to lower and lower parts of the nervous systems until in dementia and idiocy but little else than the most elementary systems of the brain presiding over vegetative and automatic functions are left-intact. This is in brief the epitome of the life-history of insanity.

As a contrast between the old and the new conceptions of investigating the scientific problems of insanity let us recur to the example mentioned in a previous chapter, where it is pointed out how futile and impossible it is to reconstruct from a few observations of the last few stages the whole life-history of the patient. Under the new conceptions of study, at our own Institute, for instance, the problem is being attacked from several standpoints. In the first place, we study the initial effects of alcohol upon the nervous system, which is not accessible to investigations confined to the asylum. We study first the exaggerated effects of alcohol where it has acted as a deadly poison, for instance in the brain of a case of fatal delirium tremens. The selection of such a case is not by any manner of means a simple matter. We have to select an individual dying of this disease in which we feel perfectly sure that the alcohol poison is not complicated with other diseases. We must find an individual whose nervous system has not begun to grow old. He must be an individual perfectly normal in all respects, so that we may be perfectly sure that what changes we find in the nervous system are due to the action of the alcohol and nothing else.

To obviate these difficulties, however, the problem becomes much simpler in the investigation of the direct action of alcohol on the nerve cells, by experimenting on animals. This is a much more satisfactory investigation in many respects than the study of the effect of alcohol on the human nervous system. For, in the animal, we can

perfectly regulate the amount given, we can stop the experiment at any stage, either at the beginning, middle or the end, and study the brain cells at all stages during the action of the alcohol.

In the light of these studies the effects of chronic alcoholism in the human being may be studied with greater profit. Here we get an inkling of the premature senility which chronic alcoholism brings about in the brain. We witness the effect of a failure on the part of the myriads of tiny constituents of the nervous system—the nerve cells—in their capacity to store energy, which they receive in the food supply from the blood vessels.

Besides this, we investigate the phenomena of intoxication in an individual to whom the alcohol is given as an experiment. We give him memory tests, discrimination tests, study the quality and intensity of sensations, the emotional character of ideas, the disorders of associations, of judgment, and, in short, devise means to measure and recount the interference with the working power of the highest powers of his nervous system. Such experiments are highly important because in the phenomena of alcoholic intoxication we have a general outline reflecting all the phases of insanity. The highest and most precious portions of our brain being the last to become evolved and educated, are also the most unstable, and are the most ready to undergo dissociation under the action of noxious stimulants. Alcohol, accordingly, begins its dissolution of the nervous system at these very highest centres of discrimination and self-control. The dissolution of the nervous system progressively descends down to lowest centres which preside over respiration and circulation, so that finally in profound intoxication the whole nervous system with the exception of the vital centres indispens-

able to the life-being of the organism is in a deep sleeping state. If the poison by alcohol proceeds too far, even the vital centres are suspended and death ensues. Thus it will be seen that in this third line of study of alcoholic insanity, the whole broad domain of the evolution and reverse dissolution of the nervous system is involved, a field conjointly demanding the attention of both the psychopathologist and cerebral anatomist.

The same problem, from the standpoint of chemistry, is approached more closely in the brains of the habitual drunkard. We endeavor to bring the methods of chemistry to bear on this problem, to see what chemical changes occur in the nerve cell in its degeneration from the habitual use of alcohol. Hand in hand with all of these investigations, are studies of the normal nervous system by the microscope, which must go on for many years before we are perfectly sure of a standard of comparison to judge of abnormal changes in the brain. At the same time other investigators are at work peering into the workings of the nerve cell in some of the humblest living creatures. For the nervous systems of the lower animals are far simpler to understand. It is much more essential to arrive at some of the fundamental laws governing the workings of the nerve cell in some of the lowest creatures than to attempt to ascertain these truths in the most complicated form of the nervous system that can be found, namely, that of man.

I can only touch in the most desultory fashion upon the great number of pathways that have to be pursued, and the great many side issues of the most profound scope, which have to be taken into consideration, in studying the initial stages of insanity. But this is the only way

we can proceed to study the more complex and advanced stages in the hospitals for the insane. This elementary sketch ought, at least, to show how many-sided the problem of insanity becomes when taken out in the outside world beyond the scope of hospitals for the insane. Such an illustration ought to show how enormously scientific investigation of the insane broadens out, even when we start at what is comparatively the simple end of the problem, namely, the study of the first phases of insanity.

To sum up the practical difficulties liable to be met with in establishing centres of scientific investigation of insanity they may be presented as follows:

1. The scientific centre must first identify and formulate its purpose and sphere of investigation; it must deliberately choose its plan before the building materials can be wisely selected; after this the laboratory or scientific centre must be given time to become equipped and organized and collect material for work; and also to apportion its general themes and special work among the members of its staff.

2. This work, from beginning to end, must take precedence of everything else and should not be interrupted by premature demands for the results of scientific work and for publications to be completed simultaneously with the organization of the laboratory, or by demands at any time for scientific research to be made to order or completed hastily.

3. The energies of the members of the staff must not be wasted in instruction that is unprofitable, or in imparting knowledge where a ground work of scientific training in general pathology, psychopathology and neurology is lacking. Instruction should only be asked when it can be

made profitable, in cases where a proper foundation has been laid previously. It requires years of instruction to supply this deficiency that ought to be made one of the requirements of entering the hospital if men are expected to do good scientific work.

If matters (2) and (3) be not held in the background pending the organization of the laboratory, or if all three of the subjects be attempted simultaneously it is quite certain that none of them can be done well, not to speak of the danger of seriously retarding the growth of the laboratory or bringing its energies to a positive standstill.

Fortunately all these drawbacks have not been encountered in the inauguration of the Pathological Institute of the New York State Hospitals. It has departed from precedent, and has been given the most cordial encouragement from its colleagues in the commission and at the hospitals, in insisting upon a broadening of the study of insanity from the modern standpoint of the correlation of many branches of science. Only through such encouragement have we been able to depart from the beaten track, and insist that the study of material within the asylums is not the whole essence of approaching the problem, and in fact constitutes but a relatively small part of the work. The scientific staff at this institute has not been hampered in the planning and direction of the scientific research work. Proper fields of inquiry are submitted to their judgment and trained discrimination. We have learned the value of the indirect study of insanity, of approaching it through a number of avenues, which, while not directly investigating the insane themselves, is infinitely more valuable at the present time.

The Institute has the opportunity of studying the conditions which lead up to the begininngs of insanity and of

observing people before they arrive at the asylum. It has been permitted to study the effects of general bodily disease upon the nervous system, and has been situated in the metropolitan centre of the State, where it might be in touch with the acute general hospitals in the investigation of the nervous system in the great mass of ordinary diseases of everyday occurrence. Its energies are not wasted by being compelled to study material which some one has selected, who does not know how it should be studied or whether such study would yield results of scientific value.

The direction of the institute has been encouraged in planning for the study of the *evolution* and the *dissolution of the nervous system.*

Provisions have been made for the psychopathological investigation of the various dissociations and syntheses of consciousness in the abnormal individual as well as experimental induction of these phenomena of consciousness in normal men and even in animals.

The plan has been followed out in collecting material, the investigation which seems, at first glance, but slightly related to the elucidation of the life-history of insanity, such as the brains of the lower and lowest creatures; autopsy material from *nervous diseases*, in contra-distinction to mental diseases; and also developing stages of animal life.

The paramount value of facilities for *animal experimentation* for the conjoint investigations of the physiological chemist and the psychopathologist of the action of *poisons* upon the nervous system has been recognized.

A very essential factor in the general plan of the work of the Institute is the necessity of providing for and stimulating research work in the study of the effects of

somatic or general bodily disease upon the nervous system. To subserve this purpose the Institute has been brought in touch through several of its associates with several of the large general hospitals in New York city, and thus has the opportunity of studying autopsy material and investigations from a psychopathological standpoint, particularly the changes in the nervous system associated with the great mass of general body diseases.

Thus we have provided facilities for investigation of the damage wrought upon the nervous system by the great host of general body diseases. This method of study, it will be seen, cannot be undertaken in the hospital for the insane. It must be followed out in the material from ordinary general hospitals and is most feasible in the large cities. The effects of the great mass of body diseases upon the nervous system are hardly at all known as yet, and most important are the results of future study in this field for the understanding of the changes in the brain going hand and hand with insanity.

The phenomena of insanity are manifold and their comprehension can only be grasped when viewed from many different standpoints—from the standpoints of many sciences. A co-operation of many sciences will bring forth a rich return of both theoretical and practical results. A many-sided, comprehensive, scientific investigation of insanity is at present an imperative necessity. We are on the threshold of a new era in the study of the nervous system in both its normal and abnormal manifestations. The inauguration of this era not only requires specialization but also interaction of the lines of research. Different branches of science must be co-ordinated and focussed together as a search-light on the mysteries of mental diseases. They must all work hand in hand.

They must be linked together and correlated, otherwise the whole aim of the work is defeated; the investigation will become one-sided and restricted, and what few facts are gained will not be open to comprehensive interpretation.

In accordance with the tenor of these prefatory remarks several departments of research ought to be established at a scientific centre for the investigation of insanity. If I may take the liberty of alluding to the scientific centre of the New York State lunacy system—the Pathological Institute of the New York State Hospitals—we may now review the purpose of these several branches of science as planned in this institution and observe the general aim of the special and combined work. Such a review, however, must be made exceedingly brief and touch on salient features only. It will at least tend to show that the microscope, far from being the principal factor of psychiatric research, plays an entirely subordinate part.

PART II.*

THE CORRELATION OF SCIENCES IN THE INVESTIGATION OF MENTAL AND NERVOUS DISEASES.

Chapter V.

NORMAL PSYCHOLOGY AND PSYCHOPATHOLOGY.

The crowning glory of psychology in these days is its emancipation from metaphysics. Psychology has become a science. It has finally shown that the phenomena of the human mind are not vague and mysterious, but that their understanding is to be gained by methods of investigation such as are pursued in elucidating the phenomena of the world of life and matter generally; by means of the same general methods of investigations used in gaining knowledge of a distant star or a tiny organism. In gaining knowledge of the physical world, we make use of patiently observed phenomena, experiments and facts, and starting out with these we work out laws and hypotheses governing these facts. Modern psychology is proceeding in the same way with the phenomena of consciousness on the inductive—deductive basis. It is hard at work at the laboratory table, gathering facts, using instruments of precision, conducting experiments, assimilating similar work from kindred branches of sciences. In brief, modern psychology is one of observation and experimentation as against speculation on the

* In this part an attempt is made to plan out in a general way the main lines of research in mental and nervous diseases without much reference to the details of their application except by way of illustration. Since the Pathological Institute of the New York State Hospitals is largely based on this plan, we take the liberty of alluding to it in the text. This Institute was established in February, 1896. The departments of normal histology of the nervous system, of experimental pathology and hæmatology, although planned some time ago, are not yet in existence, but will be established, we hope, when more work will issue from the already active departments.

nature of the soul. It is building a foundation of facts to rest the superstructure of its doctrines and generalizations and laws of phenomena of the mind. All this has been brought about practically by the development of the science in this century. Weber and Fechner founded the domain of psychophysics. Fechner particularly invented new methods to study the intensity of sensations. He studied the laws governing the relations of the intensity of sensations to their stimuli. Much of his work in particular and of the school of the psychophysicists in general, following in Fechner's steps, though highly questionable, is still useful for its *negative* results. Hemholtz contributed much to psychology by his psychophysiological studies on sensations. His magnificent intellect enabled him to apply the methods of not only one science, as physics, but to a whole group of sciences. For he was mathematician, anatomist, physiologist and a brilliant technician and worker with the microscope in unraveling the tangled fibres of the nervous system. Wundt introduced into psychology the most valuable of all methods in science, namely, the experimental method. The amount of work which Wundt has brought out from his Psychological Institute at Leipzig, most of which though giving small results, justly proclaim him as the great modern psychologist. In England, James Mill, John Stuart Mill, Bain, Spencer, Ward, Sully, Stout and others; in Italy, Mosso and others, have contributed their share to psychology. The names of Professor James and Professor Münsterberg are not to be omitted in this hasty sketch of the evolution of psychology into an exact science.

If the labors of general normal psychology have grown more scientific and practical, the work of psychopathology

or abnormal psychology, embracing the psychological study of abnormal or pathological cases, has turned out to be of special importance not only from a theoretical standpoint in revealing the inner organization of mental life, but also from a purely practical standpoint, since *it has furnished the key to the understanding and even the treatment of functional nervous and mental diseases.* The results of psychopathology, some of which were obtained in our Institute, are brilliant in the extreme; they may be considered a treasure for medical science in general and for psychiatry in particular. No psychiatrist, no neurologist, can be efficient in his respective science without a knowledge of psychopathology. Functional neurosis, that stumbling block of the medical profession in general, and of the neurologist and psychiatrist in particular, can only be intelligently studied and successfully treated through the medium of psychopathology. Psychopathology is the *sine qua non* of the science of insanity, because insanity is a manifestation of more or less persistent pathological phenomena of consciousness, and psychopathology alone possesses the methods of investigating these pathological phenomena.

The work of the French school is particularly important, because of its remarkable contribution to the science of psychopathology. The French school with Ribot, Binet, and Janet at its head has been studying man's subconscious domain, a subject of the most profound importance, not only in that it touches at the heart of man's social attributes, but that the understanding of the nature of the subconscious is absolutely essential for any intelligent conception of the origin and course of mental maladies.

Finally the brilliant psychological and especially the psychopathological studies of Dr. Sidis *on dissociations in*

consciousness, linked with the parallel physiological dissociation of different realms of the brain, marks an important stage in the progress of psychology, and particularly psychopathology. In Dr. Sidis' researches and studies of psychopathological cases, parts of the brain were dissociated from each other and the parallel psychic manifestations could be studied by themselves. Such experimental and clinical investigations help one not only to understand, but also to treat the similar isolated and split off fields of consciousness in different forms of nervous and mental diseases. Psychopathology helps to clear up hosts of difficulties that form almost insuperable obstacles in neurology and psychiatry.

Psychiatry is especially indebted to psychopathology, because it is only through the latter that psychiatry has any hopes of becoming a science relevant to its subject matter and have practical methods of treatment, based not on the rule of thumb, but on a solid scientific foundation. In fact we believe that psychopathology will ultimately replace the present would-be science of psychiatry. This sounds paradoxical, for psychiatry is generally considered to be the science of insanity. It claims the insane as its own. Unfortunately, psychiatry is a science in name only, it endeavors to be scientific, but fails in its attempt.

Psychiatry, in a certain sense, as hinted in a preceding chapter, is an overgrowth of the application of the methods of investigation of bodily diseases to those of the mind. Now it is absolutely hopeless to expect that methods applied to investigations of symptoms of somatic diseases are fit to apply to the investigation of mental maladies. These methods are absolutely incompetent, and even to a certain extent irrelevant.

The observation of the abnormal phenomena in insanity

relates to two groups of manifestations—the *somatic* and the *mental*. The *somatic* or *abnormal phenomena of the body*, including the abnormal manifestations of the lower parts of the nervous system, such as paralysis and the coarser and more obtrusive abnormal symptoms of the sense organs may be observed by the *clinical* methods of investigation. But in the study of *abnormal mental phenomena*, the disturbances of the higher forms of consciousness and the whole domain of psychomotor phenomena concomitant with dissociations of the higher spheres of the brain (where the nerve cells reach their highest complexity of organization in communities, clusters and constellations) lie beyond the scope of clinical methods of observation. These phenomena fall within the province of *pathological psychology* or *psychopathology*.

It should be more universally realized that there is a sharp dividing line between the efficacy of *clinical* and *psychopathological* methods of investigation in the study of insanity. This is an important matter, and one about which we should have clear and definite ideas in order not to make the mistake of believing that mental phenomena may be competently observed by clinical or somatic methods of investigation.

Psychiatry obeying the natural laws governing the general progress of science is still clinging to clinical investigation, in attempting to explore a territory beyond the scope of these methods. No fault is to be found with psychiatry for this state of affairs. If any criticism were justifiable, it should be regarded unfortunate that the normal psychologist has been so backward in taking up the study of pathological psychic phenomena, or psychopathology, and paving the way for the psychiatrist.

In discussing advance work in the study of abnormal organic life in the hospital, let us relegate *clinical* methods of investigation to their proper province, and not attempt the impossibility of stretching them over into the domain of abnormal mental phenomena, which can only be efficiently investigated by the methods of *psychopathology*. This same distinction between *clinical* and *psychopathological methods of investigation* deserves reflection in the study of *nervous diseases*. Psychiatry ought to embrace both fields of research in the study of insanity, the mental as well as the somatic; mamely, the investigation of the abnormal somatic phenomena and the pathological phenomena of the lower parts of the nervous system by clinical methods, and the investigation of the pathological mental phenomena by the methods of psychopathology.* It would seem appropriate, however, at present, to pin psychiatry down to the former domain where it belongs, and assign the latter to its proper sphere, pathological psychology or psychopathology. It is questionable if the psychopathologist would concede that even the pathological manifestations of the lower parts of the nervous system (and the effects of disease of these lower portions upon the higer ones), especially in functional diseases can be properly and completely investigated by the clinical methods of neuropathology and psychiatry. For all parts of the nervous system are too intimately interrelated in an organic whole to expect that the normal or pathological manifestations of these lower parts of the nervous system may be thoroughly comprehended by being isolated from the rest of the

*These methods and their application to the investigation of pathological mental manifestations are described by Dr. Sidis in a contribution from the Department of Psychology and Psychopathology now in press for a coming number of the ARCHIVES OF NEUROLOGY AND PSYCHOPATHOLOGY.

system and studied by themselves; or that the phenomena of any part of the system may be fully explained without a comprehensive knowledge of the phenomena of all other parts, the highest, the lowest, as well as the intermediate parts. Viewed in perspective the foreground of consciousness looms up beside the activity of the highest spheres of the brain composed of the most complex *constellations** of neurons while the vanishing point stretches away far down beside the activites of the lower and lowermost parts of the nervous system composed of mere elementary *groups*† of nerve cells. Thus psychopathology dealing with the pathological manifestations of consciousness *comprises a study of the phenomena of the lower parts of the nervous system* as well as of the higher portions and embraces especially the *interrelation between the two sets of phenomena in functional diseases.*

In the natural evolution of medicine, symptoms of bodily disease were worked out and differentiated first, then, after tedious halt behind all other departments of medicine, insanity was finally recognized as the symptom of abnormal conditions of the brain, and the methods of studying bodily symptoms were dragged over into the field of mental symptoms. Psychiatry in this stage of its evolution soon reached its limit of efficiency.

Psychiatry is an art and poses as a science. The science is only partially relevant to its subject. As an art it has done much. The simple recognition of the fact that insanity is a symptom of abnormal brain conditions, has overthrown the pernicious superstition of regarding the insane as possessed of devils. This alone has accomplished an enormous amount of good, and has resulted in an enlightened care of the material welfare of the patients

* Sidis, Psychology of Suggestion, Chap. XXI.
† Loc. Cit.

in our present hospitals for the insane. But we ought not mistake these advances in the art of psychiatry and think that they are scientific advances. In its wider sense, the art of psychiatry attends to the welfare of the insane as a dependent and helpless class upon the community.

The science of psychiatry deals with the whence and wherefore of mental diseases. The answer to these questions, however, psychiatry as a science, has largely failed to accomplish. A very simple and most elementary stage in the science of psychiatry was the recognition of the general fact that insanity is the symptom of pathological brain processes. This recognition rescued the insane from social revenge; at a later period from social indifference, and finally stimulated the active interference on the part of society for their welfare and humane treatment in the modern hospital of to-day. If all this progress in the art of psychiatry has been born of such an elementary and embryonic stage in its evolution as a science, how much more are we to expect in the prevention and cure of insanity in the future progress of this science? For as a science psychiatry is yet unborn, and can be brought into the world only by the aid of psychopathology. We now realize clearly the fact that writings from the standpoint of psychiatry as an art, must not pass for scientific disquisitions.

The psychiatrist on account of the incompetency of his methods is driven into the art field of psychiatry under the delusion that he is doing scientific work. Many in the field of psychiatry unconsciously bear out the criticism that scientific methods of investigating the symptoms of mental disease are merely an overgrowth of the methods used for investigating symptoms of bodily disease, by writing fine descriptions of the bodily ailments of the insane.

Fractures and dislocations of the insane are written up at length; the formation of their teeth, their palates, their hair, the occurrence of various complicating body diseases in great variety, such for instance as a fever, erysipelas, etc., are published in detail because the present psychiatric methods of investigation are better adapted to this sort of observations than for the investigation of insanity itself. Others find an opportunity for writing on medico-legal matters relating to the insane. Still others find distraction in the elaboration of statistics; others again in the field of therapeutics. Therapeutics, it is true, based on empirical knowledge of drugs has the recommendation of much common sense, because the knowledge gained thereby is founded on experience; but experience without reason is blind. The administration of drugs, particularly to the insane must rest on a rational basis, and this rational basis cannot come until we have an understanding and scientific explanation of insanity. When that time comes we may give fewer drugs, and perhaps in less quantities.

The pointing out of the unscientific character of this kind of literature may be unwelcome or unpleasant to many who are in daily touch with the insane. But if larger, broader and more inviting fields of real scientific investigation are indicated, no fault ought to be found with this presentation of the status of psychiatry. This should be reserved for those who criticise the work of the psychiatrist unintelligently, and who offer no new pathways for the old ones. It must not be understood that this pseudo scientific psychiatric literature, substituted for scientific work now possible by the advance of science, has no value. It has its peculiar interest; the only trouble with this kind of psychiatric literature is that its fields of investi-

gation are so well burrowed and harrowed out that further work is only a loss of time and labor.

The investigation of the somatic phenomena in their relation to the pathological nervous processes and mental manifestations in the insane is of vital importance not only theoretically, but also practically, because from the body is derived the nourishment and the source of energy of the nervous system. It is, therefore, of the utmost consequence to understand the relation of disorders of the body to the interferences with the food supply of the nerve cells and the influence of toxic agents on these cells. The general somatic symptoms in insanity should be rewritten and revised as often as there are new discoveries and new theories in the progress of the pathology of bodily symptoms. Moreover, the bodily symptoms in each case in the hospital as an individual, irrespective of its class grouping or particular form of insanity, should receive detailed investigation because of the importance of the relation of the body to the brain in that the former provides the food supply, the source of energy of the nerve cell. It is, however, the fluctuations of neuron energy in their relation to the mental phenomena manifested that have to be principally studied.

We must be in possession of all the knowledge possible to gain about the bodily ailments of the insane and of those things that pertain to psychiatry as an art, but many of them are indicating a tendency towards stereotyped routine in psychiatric journal literature. Frankly speaking, gynæcological affairs, sprains, dislocations and fractures, the symptomatology of mere secondary complicating diseases of the body, such as fever, etc., are really rather round-about ways of getting at the scientific investigation and explanation of the *mental symptoms in insanity*.

Statistical work still leaves much to be done that is of the utmost value. Still, all things considered, much of the literature of psychiatry, even at the present day, is far from being scientifically satisfactory.

As an example of the tangle in which psychiatry finds itself at present, one may point to the hydra-headed classifications of mental diseases with fifty-four varieties of mania, and an equal number of melancholia, given in a standard compendium. There must be something wrong with a science that finds itself in such straits. Psychiatry has no methods appropriate for the investigation of abnormal mental phenomena; what wonder that it is impotent and cannot progress. Psychiatry must broaden out. As a science, psychiatry is absolutely dependent upon psychology and psychopathology and their correlative branches of science. Psychology and psychopathology have developed the real methods for gaining the facts, observing the phenomena and conducting the experiments that psychiatry needs. The great value then of pyschology and psychopathology is paramount in reviving the suspended animation of psychiatry.

It is unfortunate that both neurologists and psychiatrists have a tendency to view psychology as so much metaphysics, or to sum up the whole practical utility of normal psychology and psychopathology with the word hypnotism, as though the sum total of the immense value of psychological and psychopathological methods of investigation and practical lessons of their teachings are bound to be centered about the phenomena of hypnosis. If there is to be any ultimate, tangible and firm basis for the understanding of mental diseases, and a consequent rational treatment and classification of them, it is surely to come as a result of the use of the methods

of psychology and psychopathology. Space forbids any more than an allusion to the great value of understanding the psychic phenomena of the normal individual by studying the disordered psychic phenomena in abnormal individuals. Scientific researches of normal mental and nervous processes seldom have their full value without the observation and experiment of pathological cases, nature's experiments. In many forms of insanity, nature is performing experiments, more ingenious and valuable for study than the psychologist, restricted to the study of the phenomena of the normal consciousness, could ever devise. Normal psychology has much to learn and in fact can itself not be firmly established without a previous thorough exploration of the domain of pathological psychology.

In one instance, at least, under the direction of Kraepelin at Heidelberg, have the results of studies in pathological psychology been most satisfactory in clearing away some of the mystery surrounding the origin of mental diseases. The extensive experiments at this school on the subject of fatigue of the nervous system have already stimulated a more exact and broader view of the study of the symptoms of insanity. But even this school has failed to study mental diseases directly at their fountain-head; it is only through such a work that we can get an insight into the nature of mental aberrations. The Department of Psychology and Psychopathology at the Institute devotes its time mostly to the study of pathological cases.

It will not be inappropriate here to make a mere allusion to three prominent cases in which the Department has not only cleared up much of the explanation of the symptoms but worked out of the laws of the

disease, the methods of cure, and applied them successfully. Psychopathology yielded definite tangible results of the highest value.

The first case was from the Binghamton State Hospital, and was studied in conjunction with Dr. William A. White. The case presented limitation of the field of vision, accompanied by occasional attacks of delirium and many other phenomena of mental dissociation. The case was closely studied experimentally; very important phenomena were elicited and a general method for the investigation and cure of similar cases discovered.

The second case was sent to the Institute through the courtesy of Professor B. Sachs, of New York city. It was one of functional hemi-anæsthesia and ataxia complicated with organic disorders. Investigation controlled and eliminated the functional disorders, which were of long standing, and had previously resisted all attempts at improvement.

The third case, known under the name of total amnesia and "double consciousness," yielded theoretical and practical discoveries of the most brilliant nature to science in general and psychology in particular. From the investigation of this case were deduced laws guiding treatment for future cases, which, up to the time of these researches, were left to the care of Providence as lying beyond the ken of human knowledge.

All of these cases were quite beyond the use of drugs, and far beyond investigation by any of the methods which neurology and psychiatry make use of, and in both cases the treatment based on theoretical studies in psychopathology was crowned with complete success.

This Department also works in the lines of *cellular psychopathology*, *correlating the different psychomotor*

manifestations with the varied affections of the neuron and fluctuations in neuron energy. This is an attempt, and the first of its kind, to bring into one comprehensive scheme and embrace in one formula *expressed in terms of the fluctuations in neuron energy with the concomitant psychomotor manifestations* the infinite number of bewildering phenomena met with in nervous and mental diseases.* Along with it the laws and principles of inter-relation of the neurons are worked out; these, we hope in due time may lead to some important laws forming the scientific basis of pathology in general, and of pathology of the nervous system in particular.

This same department in connection with that of experimental pathology and physiological chemistry is also undertaking work in comparative psychopathology. The simulacra of diseases like catalepsy, paralysis agitans or epilepsy, for instance, we are endeavoring to induce artificially in animals. The manifestations are closely studied and experimented upon, and are then correlated with nervous diseases in men that give like symptoms under the same conditions of experimentation.

This mere fleeting glimpse of the relations of psychopathology to psychiatry does not, however, regard many other great side avenues in other departments of abnormal mental and nervous life. In the prison, the reformatory, the hospital for the epileptic, in the institutions for the feeble-minded and idiots and for the general delinquent and defective mental classes psychopathology has a great field to reap. Its lines of research are the most prominent and valuable in the institutions furnishing the meeting-ground for the criminal and the victim of insanity—the

* Vide "Neuron Energy and its Psychomotor Manifestations." ARCHIVES OF NEUROLOGY AND PSYCHOPATHOLOGY, Jan., 1898.

hospital for the criminal insane. *In fact the so-called criminal anthropology is largely a domain of psychopathology*, only the physical data and measurements properly fall within the field of anthropology.

To strengthen the importance of the wider application of psychopathology in medicine by enumerating the diseases whose investigation demands its services is unnecessary since this would comprise nearly the whole great list of mental and nervous diseases. While the most brilliant domain of psychopathology is in the functional diseases of the higher realms* of the nervous system including neurasthenia, hysteria, epilepsy, etc., the investigation of the more focal or localized diseases of the nervous system and nervous diseases generally has great gains to score through the aid of pathological psychology. In nervous diseases the absence of psychopathological investigation has enforced an unfortunate negligence of the mental phenomena in these diseases. In the study of lesions of the "silent"—although to psychopathology eloquently silent—regions of the brain, especially the frontal lobes, neurological methods have made a frank confession of their defeat. In the whole group of apraxias, aphasias, amnesias and the like are inviting arenas for psychopathology. The vista of psychopathology stretches out far and wide. The science will illuminate the darkest recesses of the nervous system above all the brain.

Enough has been said to insist upon the maintenance of a Department of Psychology and Psychopathology at the scientific Institute of the New York State Hospitals, as the one the most closely affiliated with, and in fact of paramount importance in the study of insanity.

*Vide Psychopathic Waking and Sleeping States (Chart II) in "Neuron Energy," ARCHIVES, Jan., '98.

This department is provided with a reasonable outfit of instruments. It is provided with sphymographs, cardiographs, pneumographs, chronographs, ergographs, reaction-timers, etc. Some of these instruments have been made to order; others, bought in Europe. In fact, the equipping of the Department of Psychology and Psychopathology takes an amount of time which seems unintelligible to those who might expect work to come forth from an Institute of this kind with undue haste. The apparatus of this department is as yet rather meagre, and it serves only its most fundamental requirements. In the course of time, other instruments will have to be added as the department and its work will grow and develop. It cannot develop all at once and spring forth into full activity, like Minerva from the head of Jupiter. It has been thought unwise, therefore, to add apparatus to the equipment of the department beyond what is absolutely indispensable for the carrying on of the work on hand. The same is to be said of every other department in this Institute.

Within the brief space of the foundation of this department its work has grown so extensive, the problems on hand are so numerous, that an increase in its working force is absolutely essential. Without an assistant the chief of this department must lose the opportunity of taking up works of the utmost value. Psychology and psychopathology has been the central inspiration of all of the branches of research of this Institute for they have infused into the several avenues of work a spirit of philosophy, the soul of progress in any science. The department of Normal Psychology and Psychopathology is under the charge of Boris Sidis, M. A , Ph.D., (Harvard).

Chapter VI.

NORMAL HISTOLOGY OF THE NERVOUS SYSTEM.

The story of the evolution of our knowledge of the structure of the human nervous system is full of interest, if not fascination, but we can only touch upon it here in the baldest outline, sufficiently to appreciate its status at the present day.

The first and very meagre chapter containing any real insight into the marvels of the structure of the nervous system, begins with Descartes. The keenness of perception of this remarkable man enabled him long before the microscope had been invented, to portray the structure of the nerve fibres, both in diagrams and in text. He considered them as minute tubules which conveyed the animal spirits from the brain to the muscles. If we substitute for the word animal spirits the modern phrase nervous impulse, Descartes in his idea of the nerve fibres was not so very far behind our conception of this structure at the present day.

After a lapse of some three hundred years, in the early part of this century, the microscope demonstrated that the nerve fibre was not hollow, but contained a solid core, or axis. A little later in the early thirties, investigators discovered that the brain not only contained untold numbers of these nerve tubules with the solid core, but myriads and myriads of tiny lumps of protoplasm, the nerve cells.

At that day, workers in the field of the microscopical anatomy of the brain were utterly unable to solve the riddle of the relationship of the cells on the one hand and the fibres on the other. No one knew where the fibres came from, or where they ended, nor was any

one able to make out the least connection of the fibres among themselves. The whole nervous system was an inextricable snarl of an infinite number of fibres and nerve cells, hopelessly tangled and mixed up together. It was, therefore, impossible to obtain any idea as to how this greatest marvel of creation—the human brain—did its work. At this period, the microscope was in a crude condition, as compared with the powerful instrument of investigation of modern times. For to-day the construction of lenses has so advanced and their magnifying power is so great that a unit of measurement for the minute anatomist of to-day working with the microscope is only $\frac{1}{25000}$ of an inch long.

In the early thirties the brain histologist or minute anatomist had to study his material in fresh condition. He had no methods of preservation; nor did he enjoy the advantages of being able to cut thin, diaphanous slices from the brain to view under the microscope. To-day we have the whole armamentarium of the chemist to preserve the brain in a hundred different ways, which gives as many variations of methods of study. We have apparatus for cutting thin sections of the nervous system, so delicately contrived that twenty thousand of these sections piled on top of each other would not be an inch high. Moreover, to-day one has at hand a hundred aniline dyes and other colors with which to stain these sections, color and pick out selectively elements of the nervous system in the sections under the microscope so as to suit his particular purpose.

The whole record of progress in the structure of the brain invariably goes hand in hand with a similar record of improvements in the microscope and other apparatus and also in technical methods of investigation.

During the forties and fifties, investigators began to shed some light on the obscurity of the structure of the nervous system by discovering one exceedingly important fact, namely, that the cells and fibres were not independent of each other, but that the fibre was a prolongation of the cell, an outgrowth of its body. This at least cleared up the question as to the origin of the fibre, and physiologists derived comfort from this fact, in that they had a reasonable explanation of how, in a fundamental fashion, the nervous system operated. The nerve cell, so to speak, was the headquarters of nervous operations, and its enormously long outstretched arm in the form of a fibre, was a device to carry the impulse to some distant part. This important fact as to the connection of nerve fibre and nerve cell did not contribute as much toward advancing knowledge of the nervous system as might have been expected. The connection of the nerve fibre and nerve cell was only witnessed in the very simplest parts of the nervous system, and not in its more complex and most highly developed parts of the brain itself. Besides this, while the early investigators were sure that the nerve fibre came out of the nerve cell, they were still ignorant of the course and termination of the fibre. They saw the origin of one end of the fibre only, the part which sprang from the cell.

Thus until fifteen or twenty years ago the structure of the nervous system was still a riddle and a puzzle. The whole nervous system was an inextricable maze of an entangled net-work and its unraveling seemed impossible. It was hopeless confusion to attempt to follow out the pathway of a single nervous impulse in this labyrinthic net-work. Within the past ten or fifteen years the obscurity that enshrouded the nervous system was

replaced by a clear and definite insight, that is almost startling. In 1873 a distinguished Italian investigator discovered a method which revolutionized our whole knowledge of the structure of the nervous system and opened boundless fields of research in manifold directions. From the results of this method of investigation, we have a final solution of the structure of the nerve cell, the nerve fibre and their connections.

The nerve cell is like a tiny octopus. Like this animal it has a body whereby it attends to the process of digestion and assimilation. In this body, a food supply from the blood vessels is elaborated into materials which enable the cell to do its work. Like the octopus, too, from one end of the body of the nerve cell springs out a multitude of branching arms or tentacles. From another part of the cell body arises an arm different from the shorter arms or tentacles. This arm is of exceedingly great length, and passes away from the body to distances hundreds and thousands of times the diameter of the cell itself. The outstretched arms of the nerve cell octopus—the nerve fibre—may pass to the outer parts of the body, where they receive messages from the eye or ear, or other sense organs. The long arm passes out to other parts of the nervous system, to transmit impulses from one part of the nervous system to another. These octopus like nerve cells are arranged in *groups*, *systems*, *clusters*, *communities* and *constellations** of exceeding complexity.

A given nerve cell octopus passes its long outstretched arm so as to touch the tentacles or shorter arms of a second octopus. The second one, in turn, passes its long arm to the tentacles of the third and so on through an infinite set of combinations which have their highest

* Sidis, Psychology of Suggestion, Ch. XXI.

complexity of arrangement in the highest spheres of our brain, which are the last parts to develop, both in the evolution of species as well as the individual, and which are ever unstable and prone to disintegrate by reason of the process of retraction of the nerve cells.

In the lower parts of the nervous system retraction and the corresponding dissociation of the functioning groups of nerve cells is less liable to occur under the influence of pathogenic agencies. For here the functions are phylogenetically older and tend to approach more or less a stereotyped nature. Since the stability of organization of the different parts of the nervous system depends on the frequency of the impulses transmitted through the group of neurons, the lower parts of the nervous system are more firmly united than are the highest spheres of the brain.*

The most interesting feature of this latter-day conception of the make-up of the nervous system, is that the nerve cell, like the octopus, possesses power of movement over its tentacles.† Consider, for a moment, what happens when the nerve cell retracts its tentacles. The message can be no longer transmitted. The nerve cell has thrown itself out of the circuit of the long arms of its fellow-associates in a given group or community; they are no longer in contact with the retracted tentacle. But we should conceive that as a rule whole groups, communities, clusters

* This was written before Apathy's view of the concrescence of neurons came to our attention. We were thus, in a measure, prepared *a priori* to accept his views not for the whole nervous system but its lower and phylogenetically oldest portions.

† From a study of the identity of differentiation which the general structure of the neuron undergoes in the neuraxone in the form of long parallel filaments incorporated with distinct microsomes with analogous modifications of the cyto-reticulum in other somatic cells (muscle cell, ciliated cell, leucocyte, chromatophores, etc.) subservient to motility, my own observations incline me to believe that the axone may be the retractile and expansive structure of the neuron as well as the dendrons or gemmules.

and constellations of nerve cells functionally correlated retract *en masse* rather than individual cells. Cells cannot work as isolated individuals in the higher parts of the nervous system; they are invariably members of assemblages which have been physiologically linked together by education, use and function. There may be partial retraction of the individual members of one functionally linked assemblage of neurons from another assemblage, but in the phenomenon of retraction we are to picture it occurring in a mass of nerve cells belonging to some particular assemblage and occurring more or less simultaneously.

A message can no longer be delivered and transmitted from one part of the nervous system to another, if a mass of these nerve cells break the circuit by retracting their arms. This is the secret of many a puzzle and mystery enveloping a very great mass of psychomotor manifestations of the human nervous system. The object which the nerve cell apparently has in view in retracting its arms is to avoid overwork, and withdraw itself from hurtful stimuli. Retraction of the arms of the nerve cell is apparently a signal of exhaustion of the dynamic energy of the neuron.

Retraction is a remarkable adaptation of the higher order of neuron aggregates to elude stimuli (energy liberating impulses) which increasing in quantity or degree would otherwise draught off deeper and deeper levels of static neuron energy. And expenditure of static neuron energy is a process marking the passage of the psychomotor manifestations from the physiological domain to the realm of disease. In other words retraction of the neuron may be regarded as an adaptation whereby increased resistance is interposed to energy liberating

impulses which have exhausted the high potential energy stored in the neuron for the activities of the physiological waking states.

Neuron aggregates are united to each other by training, by function. The more simple the aggregates and the more frequently they functionate together the more stable is the union. The stability of the functional association is established by routine use, by habit. On the other hand the more complex are the neuron aggregates, that is the greater variety and permutations of their association with sub-aggregates, the less stable is the association. Instability of neuron aggregations reaches its *maximum* in the highest orders of constellations, for here there is but little or no permanency of the functional interaction—there is no routine beaten track, no set channels of the associations in the highest order of constellations. In a simple reflex arc the external stimuli are of a uniform kind and always proceed in the same pathway. In the highest constellations of neurons the stimuli come through a great variety of avenues. At one instant the impulse wells up through some particular avenue, at another instant the stimuli preponderate in another channel. The result is a continual flux in the functional association of the higher constellations. The functional association is subject to continual mutability, to continual forming and unforming of the associations with other neuron aggregates. This is in fact the physiological parallel of the swell and play of the human mind, the infinite variety of thought and reasoning. Association and dissociation of the higher orders of neuron aggregates may be conceived as continually taking place in *normal* mental life concomitant with the activities of the higher realms of consciousness. As Sidis explains it "under the action of the

slightest external or internal stimuli unstable systems* or constellations lose their equilibrium, dissolve and form new systems or enter into combination with other constellations. On the psychical side we have the continuous fluctuation of the content of attention. *The characteristic trait of the highest type of psychophysical life under the ordinary stimuli of the environment is a continuous process of association and dissociation of constellations.*"

Association and *dissociation* of neuron aggregates then form the physiological parallel of normal mental life. *Retraction* and *expansion* of neuron aggregates form the corresponding physiological parallel of abnormal mental life. In accordance with the laws of stability of neuron aggregations the highest and last trained constellations in the psychophysiological evolution offer the least resistance to stimuli or agencies which liberate neuron energy. If the stimulus becomes intense, or what amounts to the same thing, is persistent although of mild intensity, the most unstable constellations lose their dynamic energy first. After the dynamic energy is exhausted retraction occurs and the stimulus is evaded. Concomitantly with the retraction of the least stable constellations a sphere of consciousness is split off from the whole. If the stimulus increases still farther the retraction progresses to deeper and deeper levels in the organization of the nervous system. Clusters of neurons offering less resistance in their functional aggregation than the communities, become retracted and fall asunder. With an increase of the stimulus communities undergo dissociation among themselves and so on down to neuron aggregates which by

* By means of association fibres neuron aggregates are built up from simple to complex orders. Simple and through function firmly interwoven groups are organized into systems by association fibres. Systems are organized into communities, communities into clusters, clusters into constellations.

reason of stereotyped functional interaction are organically united. In these lowest neuron aggregates the adaptation of retraction and expansion is superfluous and might even be inimical to life.

This retraction and expansion of the arm of the nerve cell, in groups, systems and communities of brain cells, drawing it in or out of the circuit of transmission of nervous impulse, is the final unveiling of the secret of a whole host of mental phenomena which hitherto have seemed mysterious to the last degree. These attributes of extension and expansion of the nerve cell cannot fail to attract even those with the most casual interest in the operations and development of the human mind, and holds one spell-bound in the vast flood of light shed upon the explanation of insanity. Mysterious cases, for instance, of individuals who sometimes from a blow upon the head or other causes, wake up and find their past lives a blank, and who virtually begin to live their lives over again as it were, in a new world, such as a case recounted in Dr. Sidis' book "The Psychology of Suggestion" may serve as a fair example. Such cases receive their only explanation in retraction and expansion of the tentacles of the nerve cell octopus, *dissociating functioning associations of cells.*

The phenomena of hypnotism, hysteria, and of the whole great important groups of *psychopathic functional diseases* are to be explained in the same way.* Some of the violent manifestations of insanity seem to be due to the retraction of the highest constellations of nerve cells that dominate and control the lower parts of our nervous system. The lower centres being dissociated from the control of the higher ones, give rise to the phenomena found in some forms of mania (psychopathic). Discrim-

* The topic is further elaborated in the Principles of Psychopathology, a work recently completed by Dr. Sidis.

ination as to significant and insignificant stimuli is cast aside, so the maniac is prone to respond to any passing zephyr of stimulus with a storm of excitement. His subconsciousness lacks the normal control and is most prominently in the foreground.

The phenomenon of retraction of the neurons is also, I most firmly believe, the explanation of the cardinal symptoms of epilepsy in the manifestations of the fit. Here the retraction of the constellations and clusters in the higher parts (association centres of Flechsig), from a given stimulus is very sudden; the lower portions of the brain (sensory spheres of Flechsig, particulary tacto-motor zone) being suddenly loosened and dissociated from the inhibition and control of the higher portions, the energy of the neurons of these lower portions of the cortex is suddenly liberated with the corresponding psycho-motor phenomena.

Every one is familiar with those forms of insanity in which the patient seems oblivious to his outside environment, shown in some forms of melancholia (psychopathic). There are again instances where the whole foreground of consciousness has been *partially* split off by a retraction of the nerve cells constituting the higher spheres of the brain. A cleft lies between them and the rest of the nervous system, caused by this phenomena of retraction. Depending upon the quantitative degree of retraction between various assemblages of neurons in the brain some forms of psychopathic mania or melancholia might result. Thus we see that one part or another of the brain may be dissociated from the rest, and naturally the parallel manifestations of the mind are thrown out of gear.

This hasty sketch of the department devoted to the

anatomy of the nervous system, perhaps, shows best of all a faint glimpse of the directions we are striving in to contribute something toward clearing up the explanation of insanity. These introductory paragraphs ought also to show how important this department is for the investigation of insanity.

I should not, however, be guilty of conveying the impression that merely because the anatomist has discovered these wonderful facts about the shape of the nerve cell and its connections or that some evidence from my own researches tends to prove the phenomena of retraction, that the study of mental phenomena is superfluous. The anatomist, the chemist cannot possibly disclose *thought*, *consciousness* from the material phenomena with which they respectively deal. The work of the psychologist and especially of the psychopathologist attains its highest importance when the physiological processes concomitant with the mental phenomena studied are constantly kept in view. The dynamic theory of cellular life and the theory of neuron retraction in fact can be most safely worked out from the psychopathological standpoint in conjunction with the study of general physiology. The anatomist or the chemist do not have *consciousness* for their material. Thought is not a *product* of nerve cell activity in the same sense as bile is a product of the liver. The brain does not secrete thought, as the kidneys secrete urine; thought is not a material thing; it can neither be weighed nor measured. A sensation of color, for instance, as experienced by the eye, has no material existence in the physical world. We can only speak of the phenomena of consciousness as running parallel or being concomitant with the metabolism of the nerve cell, lest we make of consciousness a material body.

To the psychologist belongs the study of psychophysiological life; the details of structure fall within the sphere of the anatomist. The object of reverting back to the department of psychology and psychopathology is briefly to point out the incongruity of setting forth the claims of any of these departments of the Institute investigating insanities as distinct, isolated methods of research. They must all be linked together and work hand in hand. A concrete example of this is the apportionment and yet linking together of the work in the departments of psychology and normal anatomy of the nervous system. The psychologist, for instance, studies the manifestations concomitant with the physiological process of retraction of the tentacles of the nerve cell octopus. Working conjointly, the psychologist and the anatomist show, in an ideally scientific way, the stages of the *parallelism* of the physical process in the nerve cell and the corresponding psychic phenomena.

In the section devoted to the status of the science of pathology in investigating the nervous system, the same feature crops out again. In the abnormal anatomy of the nervous system as well as in the normal anatomy in the necessity for correlated work with psychological and psychopathological investigation is still more evident.

The anatomist, however, is not by any manner of means in a position to write the last words about the structure and architecture of the human nervous system. This goal will not be attained for many years to come. He has only been able thus far to straighten out the intricate structure and connections of the comparatively elementary chains and series of the octopus-like nerve cells in the lower and simpler parts of the nervous system. The

unravelling of the connections and associations of nerve cells in the highest parts of the nervous system, where the cells are evolved in enormous complexity of connections in the form of constellations, hardly has been begun. By studying the developing infant, however, and patiently working at the brain of the growing child, we hope to attain in the future our best light upon this obscure domain of the anatomist.

Professor Flechsig has, however, after twenty years of work, formulated a plan of the brain which, it seems to me, is the key for a final solution of the intricacies of higher brain architecture. This plan was studied out in the brains of human embryos, children at birth and growing infants, where the different parts of the nervous system can be identified because they make their appearance in a progressive series from the simple, fundamental and phylogenetically oldest parts to the more complex, highly organized and most recently evolved portions.

In accordance with this plan of Flechsig, but a small portion of the brain cortex—only one-third—comes in contact with the outside world through the chains and series of octopus-like nerve cells connecting the sense organs, while the great mass of the brain cortex—the remaining two-thirds—has no direct connection with the outer world, but connects and associates the scattered brain areas connected with the sense organs or muscles.

This division of the brain into these two parts—the smaller portion known as the sensory spheres and the larger the association centres—gives a wonderfully clear view into many forms of insanity if we take into account the concomitant psychomotor phenomena produced by different degrees of retraction of these parts, but espe-

cially by retractions occurring in the association centres themselves by retractions of communities, clusters and constellations of nerve cells.

The sensory spheres are scattered about in the cortical grey matter. A patch at the hind end of the brain is the sensory sphere for vision, another corresponding to the sensory sphere for sound is situated near the apex of the temporal lobe. Similarly olfactory, gustatory and tacto-motor sensory spheres are located in other parts of the cortex. Between the sensory spheres are interpolated the association centres. The more fundamental portions of the association centres operate to render possible a simple order of recognition of the impressions received in the sensory spheres by associating them together. In the higher regions of the association centres a still more complex order of recognition of sensory and motor impressions is possible. Finally the constellations of nerve cells probably located in the frontal lobes afford a basis for the highest forms of synthesis of consciousness. *This is the association centre of association centres.*

It is in these association centres and in their connections with the sensory spheres that the phenomena of retraction of the nerve cell plays such an important part. One can well conceive the chaotic condition of ideas, or imperfect power of recognition, and a host of other abnormal mental phenomena, when retractions occurring in the groups, communities, clusters and complex constellations of nerve cells split off the association centres, from each other or from the sensory spheres, and *produce corresponding dissociations in consciousness.* In the lower animals the association centres grow smaller and smaller, and finally, say for instance, in the lower mammals, the sensory spheres lie

contiguous with hardly any vestige of the association centres between them.

For the study of insanity, the understanding of the structure of these higher spheres of the nervous system is of the most vital importance. It is the instability of these highest parts of the nervous system which is the essence of the whole question of insanity. Hence, when we consider this aspect of the value of the department of normal histology of the nervous system, we find that its offices are absolutely indispensable.

With the exception of the discovery of the neuron theory, Sidis' psychophysiological theory of association and dissociation, the theory of the retraction and expansion of the neurons, the theory of neuron energy fluctuation, and Flechsig's plan of the association centres and sensory spheres of the brain are the greatest discoveries which have ever been put forth in the history of our knowledge of the nervous system. The effect of the application of these great hypotheses (for observations* at present in my own belief, at least, are increasing their validity) will indeed be revolutionary in the domain of mental and nervous diseases.

One standpoint in this chapter I trust is clear, and that is, we thoroughly understand that normal histology of the nervous system should not be confined to a study of the mere static side of mental and nervous life but should go hand in hand with a study of its dynamics. We cannot

* Apathy's theory of the concrescences of the neurons in the lowest parts of the nervous system may be perfectly tenable. But we should remember that the stereotyped function existing through eons of time in these lowest parts of the nervous system presupposes a fixed relation of the neurons to each other. In the evolution of the higher centres however, such as the association centres and probably the sensory spheres, the individual neurons have become independent anatomically and the impulse is transmitted by physiological contact.

Retraction does not take place in the lowest parts of the nervous system, but must be postulated for the phenomena of the highest portions of the brain. Apathy's theory, in my judgment, should not create distrust in the neuron theory; his theory does not apply to the whole nervous system, but to its lowermost parts, such as pertain to the most automatic and vegetative functions. The homologue of the lowest parts of the human nervous system is found in the leech and other invertebrates that Apathy has studied.

grasp the laws governing the dynamics of life by the study of morphology. One cannot see physiological processes in cut and dried sections through the microscope. Life phenomena are manifestations of energy. To understand the dynamic side of life phenomena one must use the principles of general physiology. For this science studies the real internal causes of the activities of living matter in energy and the laws of the equivalence of cause and effect in the phenomena of life in the liberation and restitution cycles of energy. The operations of mind however, are not modes of motion although running parallel with them. Life and matter fall within the monistic principle of energy, but mind is something apart and cannot be explained by the doctrine of energy. Physiology stands far above anatomy in its philosophy. Psychology occupies a still higher plane, for in addition to the knowledge of both that of consciousness is required.

Although realizing the great necessity of establishing the department of Normal Histology, I have not, in view of the considerable sum already expended in organizing and developing this Institute, had the temerity to ask for further expenditure in obtaining a salary for the associate in this branch until some tangible results in scientific work have been brought forth. I would now, however, *make claims for the necessity of this branch of work*, so that within the future, perhaps the ensuing year, a recommendation for its establishment may seem reasonable and fit.

It is appropriate to intimate that the associate of this line of research should pursue his studies of the normal histology of the nervous system, only after a very thorough antecedent study of the minute anatomy of all other parts of the body in order that he may be sure to have the light of analogy of the neuron with other cells of the body constantly in mind.

Chapter VII.

COMPARATIVE NEUROLOGY.

The value of the comparative study of the nervous system in both health and disease, has been hinted at in the argument for the practical value of the department of cellular biology in the scientific study of insanity. Man's nervous system is a recapitulation of the progression of development of the nervous system in animals. This recapitulation of the nervous system embracing its evolution throughout the whole animal kingdom is too complex to be understood without going back to the prologue in the history of the development in the lowest animals that possess nervous organs.

Apparently the first nucleus of a nervous system is found in the fresh water hydra. This creature can expand and retract a portion of its substance by a very simple mechanism, which is the combination of both the nervous and muscular systems. This animal appreciates stimuli from the external environment by means of a most elementary sensory apparatus, the fore-shadow of the nervous system in higher animals, and reacts by means of a primitive muscular mechanism. These two sets of mechanisms are not differentiated as in the higher animals into two distinct organizations, but are so alike and undifferentiated that it is difficult to distinguish the one from the other.

In a somewhat higher form of development, as in an ascidian, the motor and nervous systems have become differentiated. This creature has an outer tunic, an inner digestive coat and a muscular sac lying between the two. The nervous apparatus is exceedingly simple. It is merely a chain composed of very few nerve cells, one end of which

touches the outside tunic, and the other end the muscular coat. When stimuli from the external environment are conveyed to the tunic, the creature, by means of this nervous system, transmits the impulses to the muscular bag, and responds by muscular movements to these stimuli. The very simple nervous system in this creature is the fundamental basis for the building up of the nervous system in the higher animals. This tiny arc of nerve cells passing between the muscle and the skin in the ascidian is the starting point which nature builds upon in evolving the wonderfully complex nervous apparatus in higher animals and in man himself. Roughly speaking, the difference between man's nervous system and that of the ascidian is not in any essential distinction in the shape and constitution of the nerve cell, but in the fact that man possesses numerically millions and millions more, in infinitely complex adjustment, of these tiny nerve cell arcs found in the ascidian.

Passing upward in the scale of evolution from the ascidian, as more and more of these nerve cell arcs make their appearance, and are evolved into increasingly complex adjustment to each other, the animal gains more and more highly developed functions. In the lowest forms of animal life possessing the nervous system, the nerve cells are arranged in simple *chains or series*,* as the evolution of the animal grows more complex, the simple series make a greater variety of combinations with each other, so that they become gathered together into *groups*.* As the scale of evolution becomes still higher, groups of nerve cells make increasingly complex adjustments in the form of *clusters*.* In still higher forms of animal life, the adjustment of clusters

*See Sidis "Psychology of Suggestion, Chap. XXI.

of nerve cells become complicated into *communities*.* In man we find all the evolutionary series compounded into one complex whole. The elementary form of the nervous system in the lower animal represented in a simple *chain* or *series* of nerve cells, is present in the lower and more fundamental parts of his nervous system, such as the sympathetic. The more complex forms are built up into *groups*, *clusters*, *communities*, and ultimately in the highest parts of man's brain, the *communities* are gathered together in such a variety of combinations as to form an infinite number of highly complex *constellations*.*

In building up this plan of the nervous system from the lowest to the highest creatures, nature makes no sudden strides or leaps. It is a steady progression of piling up the simple series of nerve cells, such as found in the ascidian; in increasing numbers and complexity of combination until we reach the form of constellations in the highest portion of man's brain. His intellectual attainments, his highest form of consciousness, his self-control and dominance of the lower parts of his nervous system run parallel with the activities of these constellations.

Comparative anatomy of the nervous system is invaluable as a method of going back through past ages, and of witnessing how man's nervous system has been built up from the simple to the complex. All the chapters in the history of brain evolution are to come from the researches of comparative neurology. We must not expect to comprehend the architecture and phenomena of man's nervous system by considering it as something apart from the nervous system of the creatures whence he is derived. Nature did not make man's nervous system by a special *fiat*, nor in evolving it did she consider him to be any more

* See Sidis "Psychology of Suggestion," Chap. XXI.

or less than the final member of a continuous series in the progression of the evolution of life forms.

Man is to be looked upon as a creature of the past. For nature in the evolution of the nervous system has built man on the same fundamental plan with that of an ascidian. Man's nervous system is a magnificent organization, but in plan of structure it is the same in the ape, the dog or even the earth worm.

Comparative anatomy of the nervous system has often given us the most striking answers to complicated questions in man's brain. For instance, when certain animals leave their aquatic habitat and spend the rest of their existence leading a terrestrial life, special sense-organs become useless and disappear during the terrestrial life. The following out of the changes of the brain, incident to the loss of these sense-organs has thrown most important light upon some of the complicated questions of the nerves in man's brain. The enfeebled development of eyesight in the mole, and the deficient development of the portions of the brain concerned with its visual impressions have helped us in understanding the central mechanism of vision in man's brain. The enormous development of the sense of smell and of the parts of the brain devoted to the reception of olfactory impressions in the lower animals has been of much service in contributing to the knowledge of the structure of the parts of man's brain connected with his delicate but uncomprehensive sense of smell. In fact, in the study of man's brain, we are constantly driven back into the past when it was in a simpler form, in order to understand its mechanism and operations.

Comparative neurology is of value, not only in helping us to understand the architecture of the nervous system, *but it is also destined to be of great importance in imparting*

knowledge of the organization of the nerve cell as an individual, through the study of comparative cytology of the nerve cell. An individual nerve cell, a single one of the myriads and myriads composing man's brain is a microcosm taken by itself. We are far from knowing, aside from the problem of how nerve cells are connected with each other in the brain, how they work as individuals, how they live and die and pass through their whole life history. If we had the most perfect knowledge of all the combinations, adjustments and associations of the countless hosts of nerve cells in the brain, in short a perfect knowledge of the architecture, it would be of comparatively little value in the study of insanity, unless we understood the *nerve cell as an individual.* No one could build a bridge, even with the most perfect and detailed working plans, without knowing the constitution of the building materials. So it is with the nervous system. We may know much as to its architecture, and in fact are actually daily gaining more and more of this kind of knowledge by a great variety of methods, but we know comparatively little of the working units of the nervous system, the nerve cells.

The internal constitution of the nerve cells is the most pressing question of the day in the study of insanity. The all-important question is how the nerve cell works as an individual, how it conducts nervous impulses, how it assimilates food, and the mechanism of elaboration of energy from the crude food supply which the nerve cell obtains from the blood vessels. If there be one all-important question in the production of insanity, it relates to the *balance between food supply of the nerve cells* and the *work performed or withdrawal of nervous energy.* This is a practical question, because everyone knows that if more

energy is drawn off from the nerve cell than can be produced from its food supply, the result is bankruptcy of the nervous system. Anyone may see this in his daily walks of life in the man who overworks and overfatigues his nervous system. We see this debit balance in the energy of the nervous system everywhere about us in the endeavor to cheat time in the pressure of hurry and haste in the activity of large cities. People expend more energy from their nervous system than they supply through food and rest. Yet such a vitally important question as to the details of the cycles of expended energy of the nerve cell, with relation to food supply, is almost unknown. Here again we must have recourse to the aid of the comparative neurologist, but above all to the science of general physiology. We must ask him to tell us the internal structure and constitution of the nerve cells in the lower animals, because here the problem may be studied under its simplest condition. We ask him to make experiments, and to select some favorable animal to illustrate the changes of fatigue in the nerve cell, to tell us what happens when the nerve cell is deprived of its food supply, to recount to us the changes in the constitution of the nerve cell, when it is called to expend more energy than it receives in nourishment. Such questions as these are of the utmost importance.

As a concrete illustration of experimental work in comparative neurology I might mention an off-hand example in some work which we had undertaken some three years ago in the electric torpedo to determine what happened in the nerve cell when overfatigued. Two torpedoes were placed side by side. One was irritated at regular intervals with a sharp instrument, until his electric

shocks became less and less and finally disappeared. Thus the nerve cells in the brain governing the electric organ were completely tired out and could no longer work. Without giving these nerve cells time to recuperate, or to gain new energy by assimilating food from the blood vessels, the animal was killed and the cells compared under the microscope with those of the second torpedo which remained completely at rest. Thus we had side by side under the microscope, the overworked fatigued cells, and those in a perfectly normal resting condition, which had a full supply of energy. The problem was to determine not so much any outward changes in the form and shape of the cell, as its interior mechanism. Definite changes were found between the two sets of cells, changes that throw some light upon the all-important problem of how the nerve cell does its work, and carries on its life operations.

It should not be understood, however, that the fallacious view is entertained that comparative histology of the nervous system, any more than any other purely morphological study, can investigate function by merely studying shape and form. Such study is not adapted to investigate the *activities* of life. The phenomena of life are caused by mutations of energy. The analysis of life phenomena on the basis of energy should form the guiding principles of morphological studies. Morphology can get no deductive sweep over its provinces without a study of the cause of life phenomena—cycles of liberation and restitution of energy. Comparative anatomy of the nervous system must then be inspired by comparative or general physiology. Since the phenomena of consciousness may enter into the subject psychology also comes into play.

As a basis for future investigations of this department,

biological material has been collected quite extensively, more particularly marine forms.

Collections of material like these are not to be worked through blindly and merely to store facts. The facts sought for should be of qualitative rather than of quantitive value. The facts sought should be those that may be used, and to use the facts one must have some notion of the cause and effects in life phenomena. In short, comparative morphology should derive its guiding principles from the standpoint of general physiology. Morphology then becomes a philosophic study, involving the verification of causes and a fitting in of its facts with the *modus operandi* of life phenomena. Physiology contains the philosophy of morphology. Deeply impressed with this idea, I trust that comparative anatomy of the nervous system, in the plan of a coalition of sciences in psychiatric research, may be continually stimulated by the ideas of general physiology by carrying on some of its researches in the *marine biological laboratories*, such, for instance, as the one establised at Wood's Holl. During the summer season the department should transfer its work to such a centre and study the nervous system in closer relation to the general biological sciences. This branch of investigation is under the guidance of C. Judson Herrick, A. B., (Dennison University).

Chapter VIII.

DEPARTMENT OF CELLULAR BIOLOGY.

Cellular biology, lying rather remote in its field of study from the province of the asylum, those who are in touch with the insane may not wholly realize that this science forms one of the corner-stones in a rational system of investigating insanity.

The science of the cell has accomplished marvels within the past few years, and from the days of Schleiden, Schwann, Purkinje, Von Mohl and Müller vast strides have been made. Inasmuch as the whole body is a vast commonwealth of these tiny cells, some working together in a community, as in the kidney, other communities in the liver, and still others in the brain, it ought to be easy to understand that the whole ultimate solution of the workings of the body, both in health and disease, resolves itself into a study not only of the *statics* of the changes but of the *dynamics* of the individual cells themselves. Yet as Loeb, who has a profound insight into the true philosphophy of the general dynamics of life, points out* general physiology cannot be restricted to the study of special organs, nor to that of particular cells, amoebas and the like, nor can it be made identical with a study of cellular physiology unless we understand by the latter an inductive and deductive application of its laws to the *whole realm of life* phenomena. Virchow, fifty years ago, forecast that the ultimate study of disease processes, particularly in their beginning and essences, must be devoted to the cells themselves. The student of cellular biology looks upon the cell as a microcosm in itself, and his investigations have been so searching as to point to the path toward the solution of the problem of the physical basis of heredity. If the study of the cell would be rather of dynamics than that of statics, the path itself would be nearer in sight.

In studying the egg cell, just after it has started on its growth, to produce a new member of the species, the biologist has found that equivalent and equal amounts of

* Einige Bemerkungen ueber den Begriff, die geschichte und Literatur der allegemeinen Physiologie. Physiological Archives, Hull Physiological Laboratory, Vol. II.

a certain element of the cell are derived from both the father and mother. He has shown, furthermore, that these two equal and equivalent paternal and maternal elements are woven together, and by a most intricate process, distributed in equivalent amounts to every cell in the whole body. It is on this ground that Huxley says the entire organism may be compared to a web of which the warp is derived from the female, and the woof from the male. It is certainly wonderful to stand at last face to face with some intelligent and fact-supporting basis of the mechanism of heredity.

We can now have some glimpse of how immutable are the laws of heredity. This material—the germ plasm—transmitted in equal amounts from both parents to the new individual, will surely pass on damages incurred by the ancestors. If a man exposes his germ plasm to the poisonous influences of alcohol, or still worse, syphilis, such damage is not confined to his individual life only but passes on to the next generation. This damage plays a part in subtracting from the full development of the organism, especially in the most complicated tissue of the body, the nervous system. This subject of heredity is of great importance in the study of insanity, but it were well that discussions of heredity in insanity might more generally rest upon the scientific basis of our present knowledge of the germ plasm and the theories of inheritance. For if the theories be applied deductively to the phenomena of inheritance in insanity two benefits result. The facts are rearranged and marshalled in order. This being done it is to be expected that the theory will be tried and fortified. Light will then be reflected upon the theory from an inductive standpoint.

Cellular biology has also another province which cannot

be disregarded and that is embryology, which in a certain sense is correlative with the study of pathological states and conditions. The most reliable method of gaining knowledge of the architecture and function of the nervous system is to watch its growth in the successive stages of development of the embryo. Here we are able to realize the functional value of different parts of the nervous system, by studying their various stages of growth as the embryo passes through its phases of development. First, the lowest and most fundamental parts of the nervous system appear, which have to do with the mere organic and vegetative functions of the body. Little by little the higher and more complex parts appear in their turn, so that we can trace, in the growth of the embryo, chapter by chapter, the whole story of evolution in a recapitulated form. The particular value of this method lies in the fact that we are enabled to determine, in a general way, the function of different parts of the nervous system, as they make their appearance in serial order in the embryo; the lower and fundamental parts always come first, the highest and most specialized in function last. The early stages of this study of the embryology of the nervous system, naturally fall within the province of cellular biology, for it is in the developing egg that this science has gained its most brilliant achievements.

The province of cellular biology in regard to touching on the province of insanity, is so intimately linked with the scope of pathological anatomy that it is difficult to dissociate the two sciences, and discuss them separately. Briefly stated, *pathological anatomy*, or the science which treats of the structural concomitants of disease processes, *can make further progress only on condition of using the science of the cell.* I mean by the science of the cell not

only a study of its statics but also of its *dynamics*. Cellular statics is only a stepping-stone to the elaboration of the laws of energy applied to the phenomena of life.

The department of cellular biology in the modern centres for scientific investigation of the insane is absolutely indispensable. The whole study of changes wrought by disease processes in the nervous system is absolutely dependent upon the principles and methods of cellular biology. Such a department is constantly consulted by the pathologist, and it is due to this department that he is able to interpret the changed condition of the brain in disease, which he views under the microscope.

Perhaps the strongest argument for the value of cytology or cellular biology in the study of the pathology of mental diseases can be realized when we perceive that Nissl's method itself is really an outgrowth and an application of the principles and exact methods of cellular biology to the nervous system. Without in the least detracting from the fame of its discoverer and the value of his great work, Nissl's method is to be considered more as an extension of the general cytological methods of cell study to the nervous system than as an innovation in a particularized technical method. If the application of Nissl's and similar methods to the nervous system be regarded in this light—as extensions of the methods of cellular biology and requiring a knowledge of the functional organization of the nervous system when these methods are used—they can be used broadly and intelligently in the investigation of the pathology of mental diseases, and are destined to accomplish startling advances within the next decade.

Nissl's method and its congeners should be viewed as methods of cytopathology which expose the morphology

of the whole interior organization of the nerve cell in contradistinction to the crude and restrictive methods of the older pathological anatomy. These latter methods merely brought to light the external form and shape of the cells and gave an account only of the coarser and grosser morbid changes which were so far advanced as to be destructive, inducing obtrusive changes in the *external form* and *contour* of the cells. Nissl's and the cytological methods generally (for Nissl's method of staining is but one of many of these cytological methods), exposing the *internal organization* of the cells, present a hitherto entirely hidden view of structural changes parallel to the whole *normal* and *pathological metabolism* of the nerve cell; that is, as far as the process can be comprehended from a morphological standpoint unaided by the conjoint application of the general physiology. It is herein that the Nissl type of method is so valuable for investigation of the diseases of the nervous system, for we are able to see the initial stages of disease process in the *interior* of the nerve cell. But to speak of seeing stages of disease process because through the microscope we see certain alterations of structure in cells is to fall into a somewhat prevalent error of accepting descriptions of abnormal structure for explanations of pathological life activities.

Disease is a process not an entity. One must have a dynamical and not an ontological conception of it. The phenomena of disease are expressions of cycles of liberation and restitution of energy. One must have something more than a knowledge of altered structure in cells to comprehend the real process of disease. One must have a conception of the true cause of disease, namely, energy and the play of factors which

enter into its mutations which are food supply and external energy liberating impulses or stimuli, as they are called in the domain of life. The man who sticks to what he can observe through the microscope in diseased tissues will have a hard time attempting to see energy and its cycles of liberation and restitution which constitute disease processes. Therefore he hardly gets an inkling of what the whole great drama of disease really means. By the aid of the microscope the process can be indirectly verified but not directly observed. If he would know the meaning he must possess the key to the understanding of the dynamics of life, which is, that life phenomena (excepting consciousness) are mutations of energy. In short, he must use the genius of general physiology for the mental elaboration of his facts. For this science has for its province the deductive and inductive application of the laws of physics and chemistry to living matter. It should be clear, then, that we mean by cellular biology a more comprehensive standpoint than cell morphology. Its standpoint is morphology plus *general physiology*.

The whole life-history of all forms of mental and nervous disease, except the last chapters, goes hand in hand with morbid changes in the internal organization of the nerve cell. When the morbid process has gone on so far as to induce defects in the external configuration of the nerve cell, it marks the closing scenes of its life. The nerve cell then passes over into the grave; for these changes are beyond reparation; its life-history is closed, its cycles of metabolism have ceased; its delicate mechanism subservient to the expenditure and restitution of nervous energy is irrevocably damaged and no further expenditure of energy is possible, except that issuing from

the organic dissolution of the cell manifested in non-nervous energy or energy liberated in the form of heat, or chemical reactions of organic destruction. One can realize how much, then, in the morphological basis of the life-history of mental and nervous diseases has been ignored in the study of late destructive lesions of the nerve cell by the crude methods of pathological anatomy, and how much is to be learned through the services of cellular biology in donating to psychiatry and neuropathology the Nissl type of methods of investigation.

Future advances in the whole province of the pathological anatomy of mental as well as nervous diseases depends upon the application of the principles and methods of cellular biology.

One exceedingly important topic also falls within the province of cellular biology, when linked with the investigation of medical sciences, and this is the study of disease processes artificially induced in the lower animals. The lower animals, even down among the invertebrates, offer opportunities for elucidating wider and more fundamental truths concerning the cell microcosm than the higher animals, especially man.

Experimental work on these lower animals made up of relatively small colonies of cells in a simpler and more elementary form, constitutes one of the most fruitful fields of inquiry as to the behavior of the cell in the environment of disease processes. In man, and even in the higher animals, when disease processes are experimentally induced, the conditions are much more complex, so much so as to hide frequently the fundamental changes of the reaction of the cell as an individual. Since man is simply an aggregation of cells, the same general laws that govern the individual cell must also govern his organization.

The experimental induction of disease processes in the lowly and more elementary organism with a view to study the reaction of the cell in abnormal environment of pathogenic stimuli, under the simplest conditions, seems again, at first glance, to be straying from our proper pathway, the study of insanity. This, however, is not so. The nervous system is made up of myriads and myriads of these same kind of cells, marvelously compounded into one organic whole. No other cell in the whole body can compare with the nerve cell for complexity of shape and internal organization. It is not sensible to attack the problem of cell-dissolution by selecting for study the most complicated cell in the whole body. It is plain that the proper way is to study first the course of disease processes in the simpler cells. Having learned this, we can forecast what ought to happen in the complicated differentiation of the ordinary type of somatic cell into a nerve cell, and be prepared to understand what the changes in the nerve cell mean when it comes in contact with abnormal stimuli inducing disease processes.

As a general rule it is to be expected that the fundamental conceptions of cellular statics and dynamics are to be verified or induced by a study of the lower order of cellular units in the organization of the complex media of life, such as man, or in the whole scale of life itself. For the external complexities of stimuli are simpler and more controllable in the study of the lower orders of cellular units. The neuron furnishes a striking exception to the generally safe rule in solving many problems in ascending from a lower to a higher order of complexities. The neuron is the highest differention of the cell complex, yet its study furnishes an insight in the energy basis of the phenomena of life incomparably more valuable than any

other order of cells in the whole organism, or, indeed, in the whole range of life organisms. In the course of evolution it proved most useful to the organism to have in the neuron the maximum of dynamics. In seeking for the laws of the transmutations of energy as the *modus operandi* of life phenomena the study of the bacterium, the amoeba, the unicellular organisms and lower metazoa is indeed valuable, but still I think that no member of the cellular hierarchies ontogenetic or phylogenetic sheds such a flood of light on the cycles of energy liberation and restitution unfolding life phenomena, as the neuron. The study of the dynamics of the neuron furnishes the key to the energy theory of life. We may see, therefore, that a study of the highest units in life may unfold generalizing principles whose grandeur and sweep are but dimly outlined in the study of a lower order of units. The phenomena of life are most emphasized in the activities of the neuron.

We may be sure of one thing, that the nerve cell was at one time much like any of the simpler cells of the body, and that all these complex structures in the nerve cells are not new creations or *fiats* in its evolution from the simple cell, but are merely devices and modifications of the structures present in its simply organized ancestor. In other words, a cell of simple structure like the general type of somatic cell, in undergoing the phylogenetic evolution into the nerve cell, has not created new and specific elements, in order to accomplish the duties of a nerve cell, but has used its old and elementary structure and by differentiations and modifications made them fit to accomplish the offices of the nerve cell. In studying the cytopathology of the nerve cell one should hold in mind that, notwithstanding the marvelous adaptations of the cyto-

reticulum and cyto-lymph of the nerve cell wrought by evolution out of these fundamental cytologic structures common to all cells, the nerve cell should not be considered apart from the other cells of the body. The neuron is not a specific creation, it is after all a cell; its structures are homologous with other cells of humbler organization in the body, and obeys the same general basic laws governing normal and pathological metabolism like its humbler associates in the cellular body colony.

The laws which govern pathological processes (and some day these, it is to be hoped, may be expressed in terms of cell energy) operate uniformly for all of the cells of the body. The laws make no special reservations or exceptions for the cells of the nervous system, even its most highly organized spheres. Disease is one general process, but as this process manifests itself in a great variety of phases corresponding to a Protean expression of symptoms often grouping themselves in a distinct type as a distinct malady, one, therefore, must be careful not to wrongly consider the phases of the single process as individual entities and distinct processes. Various kinds of inflammations and cellular degenerations and other pathological processes should not be spoken of as individualized processes, they are merely phases of the same general process.

The more cellular biology, including both cellular statics and dynamics, is used in the study of pathological anatomy, the less tenable becomes the idea of individualizing specific morbid processes with specific diseases. When, therefore, we are attempting to study the changes in the brain, we must never forget to summon to our aid cellular biology to help us understand the meaning of the pathological processes in the nerve cells.

Let us glance for a moment at the reciprocal benefits to be gleaned from a broad union of the medical and biological sciences and especially at the *influence of the marine biological laboratories on the progress of medicine.* The value of the application of the theories of evolution as guiding principles in pathology and patho-anatomical research as well as the light reflected back on the theory of evolution urgently demands a strong, well studied rendering. I can only call attention to the subject and cannot in the least fulfill the task.

It might seem, at first sight, as if psychiatric research were straying far away from its legitimate territory in extending its work into the marine biological laboratory, but it is a sad mistake to draw lines between the medical and the biological group of sciences. Psychiatric research stands in need of the study of the neuron in its cellular individuality, and such study should be judged by general knowledge of the cell theories.

Under Professor Whitman's inspiration the Marine Biological Laboratory at Wood's Holl, Mass., is fulfilling the ideal of correlating the biological sciences. It is a school where, happily, a spirit of philosophy is in the foreground with guiding principles for the gathering of facts.

The Marine Laboratory of the United States Fish Commission, at Wood's Holl, opened again for scientific work through the broad-minded spirit of the present Commissioner, Mr. Bowers, is seeking the same ideal under the direction of Professor Bumpus, an ideal which we hope will not be abandoned, but striven after with even greater perseverance.

If the ideals of these laboratories were carried a few steps higher, by including pathology in the family of

biological sciences, the plan would be still more perfect. The phenomena of pathology and the facts of pathological anatomy are in great need of guiding principles from the theories of inheritance; of variations; of cellular adaptations: and, above all, from general physiology. For these phenomena and facts are still in confusion and have not found their full value from the standpoint of the energy basis of life phenomena. In pathology and pathological anatomy facts are greatly in excess of ideas wherewith to estimate their value.

The great question behind the study of structure is what animates the mechanism, and how is it animated, in normal or abnormal life? The question is not answered by reducing the structures to smaller and smaller units of divisibility. In passing from the grosser topographical investigation of morphological changes in organs to the individual cell or changes in the particles of the cell, pathological anatomy only evades the question. To face the problem of the *modus operandi* of disease process, one must approach the phenomena of disease from a more general standpoint and reflect on the fact that the degenerative changes in a cell are things left behind after something else has departed. *The thing which has disappeared is energy.* The changes in the dead cell do not constitute the process of disease any more than the charred remains of the gun powder constitute the explosion.

To face the problem of the dynamics of life, and this is the ultimate problem of vital phenomena, one must conceive that *all phenomena of vitality are modes of motion and that in life the same laws are operative as in the inorganic world.* In the problem of the activities of life the process of storing latent energy in the cells by assimilation

and the liberation of energy by the overcoming of resistance by other impacts of energy or stimuli must be taken into consideration. These processes cannot be grasped by study of structure alone. Other methods of investigation than the purely morphological, and different trains of thought, are required.

Yet I do not want to undervalue the study of morphology in disease. It is of the greatest value, if inspired by philosophy and a proper general groundwork for inference from the general principles of energy as the basis of life phenomena. I merely emphasize *the importance of studying function and structure hand in hand.* Medical sciences will receive their impetus from the biological sciences, from the standpoint of *function, of energy manifestations.* General physiology is indeed the central inspiration of the medical and biological sciences.

One must make use of deduction and formulate the problems before working at the facts. If the idea is wrong, its imperfections will be brought to light in the process of verification by the facts. It is better to use the facts in pathological anatomy to test theories than to have an expectation of finding some truth by delving out facts at random.

Physiology as it is generally taught in medical schools has also much to gain from the suggestive touch of the marine biological laboratory, for this form of physiology is special in its character, it is addicted to the investigation of the function of particular organs. Its specialization is somewhat at the expense of the comprehensive sweep of *general* physiology, which is not limited to organ, tissue, amoeba cell or individuals, but works out the laws of the dynamics of living matter throughout the whole realm of life.

At the same time it is to be hoped that the marine biological centres will turn their attention and devote more of their time and work not only to dead, but also, if not principally, to living cells. It is somewhat strange that studies of the living cells have been so much neglected by the morphologist, or that he had not more extensively observed the living side by side with the dead cells, and varied the environment of the former with regard to restitution and liberation of energy. It is unfortunate that many are content to believe that descriptions of mechanism are explanations of its activities.

The advantage, however, of joining the medical and biological scientific communities in a more intimate philosophical relationship by no means confers a one-sided benefit on the medical group. The biological federation of sciences and the student of evolution miss a great opportunity in neglecting comparative pathology, human pathology and pathological anatomy.

In disease the expenditure of cell energy proceeds at a faster rate, and the restitution through assimilation at a slower rate, than in normal cell life. The process is not essentially different in normal and pathological states. The difference is only in degree. In pathological processes, greater degrees of resistance are overcome, deeper levels of energy are unfolded and more intense stimuli come into play. Into the flux of all these factors enters the play of change, both of kind and degree, of the cellular food supply, and also the factor of predisposition diminishing the resistance present in normal life. The play of all of these factors opens a sweeping vista into the structural and dynamical life-history of the cell which is but dimly outlined to biologists who restrict themselves to the observation of the normal cell.

In disease external circumstances act on the cell, change the environment and call forth corresponding adaptation in the cell. In this experiment we find an opportunity of studying cellular adaptations and variations that throw some light on the theories of evolution. One point of reciprocal benefit to pathology and biology in the marine biological laboratory is an interweaving of the theories of evolution with pathological phenomena. The pathologist can hardly expect any ultimate explanation of pathological processes without having a general knowledge of the theories of evolution and heredity combined with the broad working hypothesis of the mutations of energy, applied to pathological and patho-anatomical processes.

On the other hand, the student of biology may have a flood of light reflected upon the theory of evolution by including the domain of disease within his horizon. The theory of evolution takes account mainly of external configuration or gross morphology with respect to phylogeny. Variation and its growth with selection must have similar underlying modifications in the cells. The fundamental factors creating phylogenetic variations in cells are food supply, the storing of energy in the cell and energy liberating impulses or stimuli, which overcome resistances and set free the latent energy in the cell. The play of all these factors in creating variations in the cell is most prominently brought to the surface in the observation of pathological cellular processes. The principles of evolution should be carried more extensively into the province of the cell considered as a chemical machine, through which energy is stored from food supply and liberated by the agencies of stimuli overcoming resistance.

The germ plasm is to be considered the same way. Changes in environment is the great modifying factor in

evolution. These disturb the external circumstances, modify both food supply and stimulus, and hence modify the cell itself, and determine the persistence of the variation as an adaptation. Since the phenomena are mutations of energy, morphology alone cannot fully grasp them. The great field for future studies in evolution is pathology, or rather pathological physiology.

The study of evolution has passed to the investigation of the cell. Much of this, although greatly centered about the egg cell and its immediate progeny in ontogeny, also takes account of phylogeny. Still the study of the cell is not sufficiently illumined by the energy basis of life phenomena. The study of evolution depends too much on morphology, and too little on general physiology.

At present there is a growing demand for a sounder and more extensive inductive basis for the study of evolution. This is realized for instance in the work of DeVarigny. In the problems of life, however, too great a reliance on the inductive method is unsafe, because of the mutiplicity and conflicting nature of the proximate causes. The causes themselves have to be regarded deductively. In extending the study of evolution into the domain of pathology there is opportunity for a keen, powerful weapon of thought in an intimate union of both methods. On the one hand is the ultimate cause, energy, the guiding principle for deduction; on the other are the most magnificent experiments of nature in disease processes, as a basis for the inductive method. By the reaction of each method on the other, I think that the expectation is not exaggerated that evolution would gain a new standpoint of thought as startling as that of Darwin's.

There is a particular reason why the study of evolution should consider human pathology, because of our knowledge of man's psycho-physiological life. Pathology (the study of the dynamics of disease process) and pathological anatomy (the study of the structural alterations in disease) are in much the same position as the biological sciences at the time of Darwin. If a second Darwin could arise for the pathological sciences, he would find the storehouses of these sciences almost bursting with facts requiring generalization. The Darwin of pathology will find the suitable environment for his genius in general physiology. From its principles, he will descend upon the phenomena of pathology, and the facts of pathological anatomy, and weave out of them not only a classified, but a consistent body of knowledge in relation to the laws of energy. He will not be confused by founding his deductive basis on the proximate causes of disease, the energy liberating stimuli, but will have the ultimate cause of morbid processes—cell energy—as a commanding eminence to survey the majestic drama of disease. The uttermost details of structural changes will not be of vital concern to him, nor will the finding of the uttermost explanation of the source of energy itself interfere with the consummation of his ordained work. He will conceive that the laws of evolution pertaining to the organism as a whole also hold sway over the individual cells. He will perceive that the same struggle for food supply in the outside world goes on in the body in the growth of its units. He will see the perishing of the weak cells in disease and the survival of the stronger ones with greater degrees of resistance to liberating impulses. In brief, this man will possess a two-edged weapon with the deductive principle of energy on one side, and the great experiments of disease as an

inductive standpoint on the other. With it he will wrest out great victories for pathology and perhaps still greater triumphs for the theory of evolution.

If the pathological anatomist would borrow a suggestion from the theory of evolution with its fundamental principle of the struggle of organisms for food supply, he would get a broad hint of the explanation of hyperplasia. He would at least see the hollowness of certain glib phrases which simply gloss over the difficulties.

The physician, the clinician, the practitioner whom the "scientific" laboratory pathologist regards as unscientific stands nearer the fountainhead of disease and is in a far better position to observe and follow the energy mutations of pathological processes than his colleague, the pathological anatomist. This which seems at first sight rather strange, if not paradoxical, is not at all surprising. For the reflective physician is really a physiologist, or to make a rather unnecessary distinction, a pathological physiologist. He observes the living phenomena, and manifestations of liberation of energy are obtrusively and dramatically put before him every day in rise of temperature, convulsions, œdema, delirium, the epileptic fit, and manifold other phenomena of liberations and restitutions of energy, called symptoms. He has an idea, vague and unformulated though, of the coming to the surface of the energies of life in disease. The pathological anatomist, however, sees nothing but the husk and the shell of something that has gone. He sees hieroglyphics graven on tissue or cell, but he is not able to interpret them until he knows of the invisible force that wrote them.

I think, then, that the influence of a closer union of biology and evolution on the progress of medical sciences

becomes deeper and more important the further we go beneath the surface of things, the more we realize that the great inspiration to scientific progress is in new ideas, new trains of thought, and altogether in the subordination of observation and experimentation to guiding principles.

If the general subject of pathology profits by affiliation with the ideas governing biological research, psychopathology must gain as well, and likewise the subdivision of pathology which is concerned with nervous diseases. The marine biological centres at Wood's Holl concentrate a wide diversity of attention on the biological sciences. Representative men in all provinces of biology from nearly all the prominent universities in the United States gather at these centres. By means of lectures, conferences, seminars, individual discussions, ideas are exchanged and the results of research compared. The danger of isolation in work is warded off. Fortunately as this Institute is but a few hours away from these centres, and as they are essentially summer schools, no practical difficulties stand in the way of profiting by the far-reaching influence of the biological sciences upon the progress of the medical sciences and especially on psychiatry. We have recommended, therefore, that during the summer season the departments of cellular biology and comparative histology of the nervous system should transfer their work to these biological centres of research.

A most unfortunate gap lies between cellular biology and the pathological anatomy of the human body—cytopathology—a term but newly coined. I do not hesitate to say that the overlapping of cellular biology and pathological anatomy opens the richest of all domains for the future progress of medical science. If our endeavors to bridge over these two fields of science, so that they may work

hand in hand, be made plain, I need say little more to defend the importance of cellular biology as one of the most powerful factors that contribute to successful organization of a centre for scientific investigation of the insane.

The department is under the guidance of Arnold Graf,* Ph. D. (Zürich).

Chapter IX.

PATHOLOGICAL ANATOMY, BACTERIOLOGY AND PHYSIOLOGICAL CHEMISTRY.

The departments of Pathological Anatomy, Bacteriology and Physiological Chemistry are so intimately linked together in the investigation of insanity that they may be dealt with collectively.

Pathology being the science concerning the origin, course and results of disease, had very simple beginnings. At first evil humors were supposed to gain access to the blood and to cause the departures from health. If we translate the term "humors" into the modern expression of toxic substances circulating in the blood, the older pathologists are not so far from the truth as regards the proximate causes of disease. But whence the humors arose and how they gained access

* As these sheets are passing through the press we are struck by the sad tidings of Dr. Graf's untimely death. This is a deep loss to the science of biology, especially in the field of cytology and cytopathology. Dr. Graf's great work, "Hirudinien Studien," including his theory of the physiology of excretion is being published by the Leopold Carolina Academy. His last work, Studies on the Nucleolus, will be edited by Professor T. H. Montgomery, and appear shortly. His work on fatigue of motor neurons in certain chelonians, his researches in the cytology of the human nervous system in a case of a criminal executed by electricity and his studies on the subject of the excretion of metaplasm granules in the neuron under pathological conditions, the latter undertaken conjointly with another investigator, are left unfinished. Unfortunately these latter works are left as fragments, and it may be impossible to collect them for record. An account of Dr. Graf's life and genius is now in preparation.

to the blood was all guesswork and speculation, and "humoral" pathology was a mere makeshift to define an unknown something which circulated in the blood and set free the phenomena of disease. In later days those who were concerned in the investigation of disease processes observed with the naked eye what they could of the changes in the body after death from any given disease, and were able to see that many of the symptoms corresponded to gross, coarse and destructive changes in the various organs. As the microscope improved, and ideas of the cell as the elementary unit of the whole body became more definite and coherent, the pathologist studied these coarser and grosser changes in the organs under the microscope, but even here he saw results rather than beginnings of the processes. The observation of some final members of a series of *morphological* changes could hardly give any idea of the whole complicated range of the antecedent members, much less furnish any explanation of the true cause of these effects and its *modus operandi* in manifesting abnormal *function* in disease. Professor Prudden quotes a line from Oliver Wendell Holmes, in which the work of the earlier pathologist is compared to an inspection of the fireworks on the morning after the show.

In those days the practising physician was also the pathological anatomist. He combined both functions. He observed disease in the living and sought to find its havoc amid the body structures after death. His methods, however, were limited to the study of the topography of the lesions of the disease, and *not to the pathological processes themselves constituting it.* In short, he saw results, but knew not whence and how they came. For the origin of these morphological concomitants of disease processes can be found, not in the gross and terminal

changes in great communities and masses of cells, but within the subtle recesses of the cells as individuals.

For many years the pathologist went along bewildered by the phenomena of inflammation. He was able to describe with much precision facts and observations, but he failed to understand their significance. Meanwhile cellular biology progressed with rapid strides and disclosed the marvels of the cell microcosm. The older pathological anatomist was in somewhat of a Rip Van Winkle attitude pending this march of cellular biology, and awoke in bewilderment at finding that all his work in the study of morbid structural changes stopped short of the real origin within the cell as an individual. He neglected the beginning and saw only the end.

The advances in cellular biology are destined to give an enormous impetus to the future investigations of pathology. What, perhaps, puzzled the pathologist the most, before he had learned to peer into the cell microcosm for the solution of his problems, was the great number of important and serious diseases of everyday occurrence which seemed to leave no traces whatsoever upon the body. This was especially the case in many diseases of the nervous system. It was exceedingly perplexing, for instance, to understand how such a dramatic and dreaded attack of the nervous system as hydrophobia should leave no traces after death. The same might be said of epilepsy and many forms of insanity. These the pathological anatomist set down as diseases "*sine materia*" or cast them into the makeshift category of "functional" or idiopathic diseases. To-day, however, we are in a more fortunate position to understand why it seemed that no traces were left in the body from such serious diseases as these. The *secret lies in changes in the very inmost recesses of the nerve cells themselves.*

The older patho-anatomist concerned himself but little with the cell as an individual. If its shape, form and contour were unchanged, it passed muster as sound and normal, without regard to a whole world of changes which might be present in its internal organization. In scrutinizing the effects of disease he looked at the outside of the cell, and not at its vital organization within, as one might attempt to understand the contents of a book by looking at its binding. Thus, naturally enough, the knowledge of the structural changes of a whole host of diseases, particularly of the nervous system, was passed over unnoticed.

It is different to-day. The pathologist has borrowed the searching methods of the modern cellular biologist, who looks into the inner constitution of the cell and beholds a world of changes in the cell in general, and in the nerve cell in particular—changes which until now were entirely ignored. At the present time the anatomist in stuyding the diseases of the nervous system is actually peering into the mechanism of life operations going on in the laboratory of the cell. He is endeavoring to study the changes in the body of the nerve cell—changes going hand in hand with its assimilation of food and elaboration of energy. He is able to study the changes which happen within the cell when its food supply is interrupted or interfered with. Through this refined study of the organization of the neuron cell body—the headquarters of operations in the cycles of neuron metabolism—we realize that the oft recurring phenomenon of nerve fibre death so characteristic of subacute and chronic diseases of the brain and nervous system, is not the result of primary processes in the nerve fibre itself or in the surrounding neuroglia elements, but is entirely

the secondary effect of lesions in the interior of the cell body.

When the food supply of the nerve cell is by slight increments qualitatively or quantitatively diminished, or, on the other hand, the nerve cell expends more energy—in states of pathological fatigue—than can be recruited from the food supply in the blood plasma, the nerve casts off *dead material* which is removed by the lymphatics. The excretion of these particles—*the metaplasm granules**—is most important in presenting a physical basis and a measure of the slow destructive pathological metabolism of the nerve cell which is such a prominent factor in the genesis of very many mental and nervous diseases. When the nerve cell begins to excrete these particles it is an indication of a lack of balance between the crude food supply of the cell from the blood vessels and the expenditure of energy. This *excretion of the nerve cell* is also the indication of senile degeneration, and it is most interesting to view this indication of senility of the nerve cell advancing prematurely in a host of mental and nervous diseases where the expenditure of energy of the nerve cell has been of a pathological and persistent character.

The excretion of the mataplasm granules is an indication of the slow, gradual and long continued liberation of neuron energy. The appearance of these granules seems a sure indication that the descending metabolism has gained vantage over the ascending process and little by little lower and lower levels of neuron energy are drawn off. Hand in hand with this the neuraxon dies. First the peripheral end dies and ascending metabolism becoming

* Van Gieson: Toxic Basis of Neural Diseases. State Hospitals Bulletin, 1897. To be continued in these ARCHIVES.

continually of shorter range the death of the fibre from lack of food supply from the neuron cell body continually approaches the cell body. In the decrease of the range of restitution of energy a shorter length of the neuraxon can be supplied with energy. In peripheral neuritis, in tabes, in general paresis, in amyotrophic lateral sclerosis, in pernicious anæmia, in chronic alcoholism and under many other conditions numerous observations of the excretion of metaplasm granules from the neuron cell body confirm my conception of the nature of nerve fibre death.

The excretion of metaplasm granules from the neuron cell body means that the tide of neuron energy is slowly ebbing away. Each incoming wave of restitution of energy may indeed almost rise to the level of the preceding outgoing wave of liberation of energy, but in time, if there be no turning point where flood outmasters ebb, the neuron is marked for destruction.

The most important bearing of the discovery (unless by this time it be well known) of the excretion of the neuron under pathological conditions is the indication of deficient food supply. This is a factor of profound importance in the genesis of mental and nervous diseases, and is also of extensive application. During life we have at present no adequate means of determining the factor of deficient food supply to the neuron cell body, nor can we fully realize how often mental and nervous diseases depend upon this factor which virtually means declining capacity or the storing of neuron energy. In the excretion of metaplasm granules from the neuron cell body (and especially in motor cells, *the migration of the nucleus*) we have a new and very delicate proof of deficient food supply for the nerve cells. If in the future we shall be able to determine a means of indicating the excretion of the ganglion cell during life

by the tests of the physiological chemist,* another discovery of the utmost practical importance will be added to this great question of the variations of food supply for the neurons.

I do not hesitate to say, therefore, that the *metaplasm excretion* of the neuron, the working out of its significance and that of the *migration of the nucleus* are discoveries not only of considerable theoretical, but also of practical importance. Of course the length of the fibre and the relative amount of work done by various neuron aggregates enter into the discussion of deficient food supply of the neuron. These points, although of much importance, can here only be hinted at and must be taken up elsewhere.

The pathologist is now busily seeking the degenerations occurring in the interior of the ganglion cell when exposed to poisons, especially to those generated in the great mass of general body diseases. In the poisoning of the nervous system from general body disease, the pathologist is able to show changes within the interior of the nerve cell which go hand in hand with the liberation of neuron energy in the delirium in typhoid fever, influenza, sunstroke, etc.

We are able in these days, thanks to the aid of cellular biology and its methods, to study the changes in the nerve cell wrought by fatigue, to watch the nerve cell grow old and perceive the signs that indicate the approach of its decadence. It is particularly interesting to watch the *premature senility* and shortening of the life of the nerve cell by chronic *alcoholism* and *syphilis*.

Definite laws of the fluctuations of neuron energy, the

* I have already suggested this problem to the Department of Physiological Chemistry and the work is under way, beginning, if possible, with the chemical identification of the neuron metaplasm.

expenditure of energy of the diseased nerve cell, the restitution of energy in recovery from disease, with their concomitant psychomotor manifestations formulated at this Institute are helping to clear away the mystery of the modus operandi of a whole host of mental and nervous diseases.*

The rise of bacteriology is too familiar and of too recent occurrence to need any detailed account of its relation to pathological researches in the nervous system. Bacteriology in its great public practical services to sanitation, its application by boards of health in the prevention of infectious diseases, the almost miraculous practical outcome of bacteriological studies in the anti-toxine treatment of diphtheria, its great service in protecting and forewarning the healthy against disease, all these one cannot help acknowledging as being of great benefit to humanity. The services of bacteriology show clearly that it is an important department in medicine for finding the proximate causes of morbid processes and thus indicating practical measures to the prevention of disease.

The department of bacteriology, it should be expressly understood, does not undertake to carry on researches in the whole domain of the biology of bacteria in general, but restricts its energies to useful ends in the study of insanity, namely, the identification of bacterial poisons associated with nervous or mental diseases. This department, however, keeps in constant touch with the broader aspect of bacteriology in general, as a science, and keeps cultures of many forms of bacteria for the purpose of determining, experimentally, the action of their poisons upon the nervous system of animals.

*Vide "Neuron Energy and its Psychomotor Manifestations," ARCHIVES, Vol. I, No. 1. A further study will appear in the ARCHIVES in monograph form.

When the pathologist beheld the action of these disease-producing bacteria, he at last began to approach the proximate explanation of many morbid processes. He now sees that these disease processes are liberations and restitutions of static cell energy initiated by chemical reactions between the cell molecules storing latent cell energy on the one hand and forms of energy liberating impulses embodied in poisons and other pathologenic stimuli. The cell stores latent energy by assimilation in building up its complex molecules. This energy is set free by impacts of kinetic energy acting on the cells from without. These external impacts of energy acting on the latent cell energy are stimuli or energy liberating forces. These stimuli are comparable to the spark which ignites gunpowder and liberates its energy. The spark is not the true cause of the explosion. The true cause is the latent energy of the gunpowder itself. The spark is a liberating impact. It is an impingement of active energy on latent energy overcoming its resistance and thereby setting it free. If the latent energy of a cell is easily liberated the resistance is correspondingly small. If the cell energy is liberated with difficulty, that is, if it requires a strong liberating impulse or stimulus, its resistance is great. Bacterial and other poisons overcome resistances of latent cell energy beyond the range necessary for response to the stimuli of normal physiological life. Bacterial and other pathogenic poisons are energy liberating impulses. They seem to operate on the cell by chemical reactions whereby the cell molecules are reduced to lower and lower orders of complexity of organization. With each descent in the tearing down of the cell molecules more energy is liberated and also more resistance interposed. Predisposition, which means a diminution of resistance, is a pivotal factor

in pathological ranges of energy liberation, but the consideration of this factor is full of difficulties. *The process of disease should in the future be discussed in terms of fluctuations of cell energy.*

As a rule bacteria are not harmful by their mere mechanical presence, but on account of the powerful poisons which they give rise to. It now seems that inflammation is the expression of a conflict between the cells of the body on the one hand and the bacteria with their associated poisons on the other. The idea of a conflict, however, in inflammation between cells and bacteria is somewhat unfortunate, for it hides a broader explanation of the phenomenon which can be better understood by thinking of the relation of cells to their food supply—and the energy basis of disease processes in general.

The conservative nature of disease processes is most beautifully shown in inflammation. Inflammation is found to be a protective mechanism in the struggle of the organism for its life existence, and is the outcome of a long series of adaptations on the part of the cell. This protective mechanism against the proximate causes of diseases extends throughout the whole scale of animal life, even to the amoeba. Were it not for this protective adaptation on the part of the body cells, the highly organized forms of animal life, as well as the human race, could not exist, for by long odds the conditions producing disease are in the ascendant over those contributing to normal life.

We must not, however, overestimate the direct bearing of bacteriology on the study of insanity. Bacteria are very seldom directly responsible for mental maladies, and comparatively rarely for nervous diseases. They do not attack the brain directly, nor is it to be supposed that

there are specific bacteria for individual diseases of the nervous system. The action of bacteria in damaging the nervous system is indirect. The brain is so well protected against their incursions, that they generally attack some other part of the body. The nervous system is injured by the *poisons* which bacteria give rise to. The bacterial products enter the circulation or lymph spaces, come in contact with the nerve cells, and poison them, that is liberate neuron energy. Not an inconsiderable share of diseases of the nervous system in general take their primary origin in bodily diseases. These general body diseases, such as typhoid fever, pneumonia, syphilis, small-pox, influenza, scarlet fever, etc., either by their poisons or by interference with the food supply of the nerve cell, cause it to degenerate. In short, bacteriology and pathological anatomy are closely interrelated. It is not alone sufficient for the pathologist to recount the subtle changes occurring within the nerve cell in disease and render an opinion, to the effect that these changes are due to the action of a poison. We must know what the poison is, and where it comes from. In the solution of this question, bacteriology and physiological chemistry are indispensable.

The physiological chemist goes far deeper than the bacteriologist in identifying the proximate pathogenic stimuli. The devotees of medical science, particularly of pathological anatomy and pathology, are turning in eager anticipation to the science of physiological chemistry for a deeper solution of the question of concomitance of chemical changes and cell degenerations. What the pathologist observes under the microscope even in the most delicate changes of cell organization, is really far short of a causal explanation of disease processes. Behind all these morphological changes in the cell is a series

of most complex chemical adjustments, and behind these adjustments or concomitant with them are the cycles of liberation and restitution of cell energy.

All diseases as well as normal processes run parallel to cycles of chemical analysis and synthesis in the cell. Cell chemistry is still in its infancy. Its great motive is to furnish the chemical steps of normal and pathological metabolism of the cell concurrent with the corresponding cycles of energy. It is by means of this science that we can have any hopes of discovering the chemical composition of the cell; the reactions of the cells to poisons; the nature of these pathogenic poisons themselves, their origin, their interference with the food supply provided by the blood to the cells for the elaboration of their energy. When all these problems are solved, the abnormal changes in cells, seen under the microscope, will be more fully explained, because we shall be better able to assign to such changes their dynamical valuation. The province of physiological chemistry is the connecting link between the concomitance of pathological cycles of cell energy liberation and restitution on the one hand and structural changes on the other. Beside each increment or decrement in cell energy I imagine a corresponding chemical (or physical) change, and beside each chemical change, a corresponding physical alteration. But what we see of structural changes under the microscope must be very fragmentary counterparts of the chemical changes parallel to the energy fluctuations in the cell.

As physiological chemistry advances it would seem that a more complete series of the chemical concomitants of cell energy fluctuations would be furnished than can ever be given of the structural effects of these fluctuations of cell energy by morphology. While physiological chemistry is

striving to fill up the gap between structural changes and cell energy fluctuations, it seems best to apply the theory of cell energy deductively to pathological cell changes and describe these changes as effects of cell energy fluctuations.

Physiological chemistry has its specific *rôle* in the investigation of insanity. Few of us realize the fact that at every moment of our lives poisons are generated in the body itself, poisons which in health are taken care of and eliminated. When, however, some slight hitch occurs in the delicate equilibrium of the chemical reactions going on in the complicated laboratory of the body, widespread havoc may occur. A poison generated within the body may escape into the blood, and while it may do comparatively little damage to the more lowly organized and more resistent body cells, it may still harm the sensitive and highly organized nerve cells. Of all parts of the body the nervous system is the most sensitive to toxic substances. The sensitivity of the nervous system to pathogenic stimuli make it a delicate index of the presence of poisons generated within the body itself.

The conviction is daily gaining ground that many forms of insanity which arise so insidiously are initiated by self-poisoning. The microscope may show us traces of these poisons on the cell, but their source and nature can only be discovered by the methods of physiological chemistry. The microscope is, no doubt, powerful, but it cannot penetrate into the depths which physiological chemistry can reveal. Beyond a certain region of morphological research into the mechanism of the nervous system, the microscope alone proves an utter failure. These poisons generated by the body are of such subtle origin that it would seem almost beyond the power of science to identify or trace them. The physiological chemist attempts to identify

them by examining the secretions, or the blood. If unable to identify and separate them directly from other components of the body fluids, he is still able to indicate their presence—he injects the body fluids into animals and watches the physiological effects by which he is enabled to tell whether the body is generating poisonous matters.

In identifying the poisons associated with bacteria the researches of the physiological chemist have been attended in many instances with brilliant success. In tetanus, for instance, the bacteriologist at first identified the bacteria of tetanus, has studied their whole life-history and habits, and has even found this germ in the wilds of Africa, where the natives smear their arrows with mud of certain swamps which become partially dry during the summer season. This earth contains the spores of the tetanus bacillus, and thus the strange fact explains why the victims struck by their arrows often die of tetanus.

The physiological chemist, however, has gone further than this. He has succeeded in isolating the poisonous principles associated with the tetanus bacillus, and is actually able to separate them in the form of a powder so that one might carry round in his vest pocket a real liberating agent of tetanus, were it not so sinister a substance and so extraordinary a poison, for 0.065 of a gramme is absolutely fatal to animal life. Such a poison transcends in intensity almost anything that we know of among drugs and inorganic poisons. A little of the tetanus bacillus poison goes a good way, and it is not unlikely that many other bacterial poisons are almost as powerful. The poisons formed within the body itself seem to be less fulgerant in their action; they are mild in intensity and operate insidiously; but, unfortunately, they offset this mildness by their tendency to remain persistent. This

presents a great barrier to the restitution of the nerve cell, for it is deprived of an opportunity to rest and recover its pathological expenditure of energy.

Seeing that not an inconsiderable proportion of mental diseases is initiated by the action of poisons upon the nervous system, especially those of general bodily disease, it is of the utmost importance to trace them and use, as far as possible, practical measures against them. I think, therefore, that pathological anatomy, bacteriology and especially physiological chemistry need no further words of explanation of their place in the investigation of insanity.

We must not, however, fall into the error of believing that the researches of pathological anatomy, bacteriology and physiological chemistry, no matter how brilliant or searching they are, can give any explanation of insanity. If proximate causes of certain phases of insanity, mere neuron energy liberating impulses, are discovered in the form of toxines and bacteria, the *modus operandi* of abnormal mental life is not all explained. The discovery of these proximate causes is, no doubt, of great benefit from the standpoint of treatment, but this, however, is far from being sufficient, something more remains to be accomplished. We must *explain* the phenomena as well as the agents which set them in operation. Least of all can the microscopic study of fragmentary morphological traces of the ebb and flow of neuron energy furnish so much as an inkling of abnormal mental life. It is really time that the idea of patterning psychiatric research after medical investigation were abandoned.

If we wish to gain an explanation of insanity it must be plain that the first and main thing to do is to study insanity itself, to investigate the living phenomena of

abnormal mental life. This the branches of medical research cannot accomplish. The phenomena of consciousness are beyond the grasp of medical sciences, and it is a delusion for medicine to pretend that it can investigate mental life. This belongs to psychology. Psychological investigation of abnormal mental phenomena themselves will furnish guiding principle of the *modus operandi* of insanity. Once this is accomplished the various medical and biological branches immediately fall in line; their investigation subserve a purpose and can be guided to bear on the explanation of insanity. Psychiatry can go on indefinitely under the guidance of the medical conception of research and profit only by piling up inco-ordinated details of anatomical, physiological and chemico-physiological observations, if this be of any real scientific profit, and still be no nearer to any great co-ordinating principle of the phenomena of abnormal mental life. The most that can be gained by the present medical methods is the discovery of some of the proximate causes without attaining at any real insight into the nature of the psychopathological processes that give rise to the symptoms of mental diseases.

With all of these wonderful avenues of investigation recently opened in the research of nervous and mental diseases, when it comes to the *explanation* of the phenomena of abnormal mental life, neither the pathologist, nor the physiological chemist, nor the bacteriologist can go beyond the mere description of facts and observations. *The real meaning of the great majority of all the changes in the nervous system, in mental maladies, the significance of the manifestations associated with these changes during the life of the patient can only be made clear through the science of psychopathology.*

The futility of attempting to understand the workings of consciousness by the medical conception of becoming familiar with its mere utensils,—through the study of anatomy, physiology and chemistry is charmingly expressed by Professor Ewald Hering's fine essay "On Memory and the Specific Energies of the Nervous System:" "The nervous system, and above all, the brain, is the grand tool-house of consciousness. Each one of the cerebral elements is a particular tool. Consciousness may be likened to a workingman whose tools gradually become so numerous, so various, and so specialized that he has for every detail of his work a tool which is especially adapted to perform just this kind of work most easily and accurately. If he loses a tool he still possesses a thousand other tools to do the same work, although with more difficulty and loss of time. Should he lose these thousand also he might still retain hundreds with which he can possibly do his work still, but the difficulty increases. He must have lost a very large number of his tools if certain actions become absolutely impossible."

"The knowledge of the tools alone does not suffice to ascertain what work is performed by the tools. The anatomist, therefore, will never understand the labyrinth of cerebral cells and fibres, and the physiologist will never comprehend the thousand-fold action of its irritations, unless they succeed in resolving the phenomena of consciousness into these elements in order to obtain from the kind and strength, from the progression and connection of our perceptions, sensations and conceptions, a clear idea about the kind and progression of the material processes in the brain. Without this clue the brain will always be a closed book."

"We can, indeed, compare the brain to a book. A

book is anatomically a number of rectangular white leaves, bound on one side, and marked on their pages with numerous black spots of different form and size. Under a microscope the leaves will be seen to consist of delicate fibres, and the black spots of minute black granules. A chemical analysis will show that the leaves are cellulose and the spots carbon and resinous oil. If all has been investigated and ascertained with the utmost accuracy, we do not know, in the least, why the black spots are arranged just in this and in no other way, why some spots are large and others small, why some occur frequently, others rarely, why the single leaves follow one another in this and in no other order, and altogether what the book really *means*."

"Whoever wishes to know what the book signifies must know what is the function of the specific energy of each single letter and of the individual energy of each single word—in short, he must know how to read."

The interpretation of the book is indeed sealed to purely medical methods, notwithstanding the amount of analysis that may be performed by the mainstays of medical research. To know how to read the book we must turn to the science of the phenomena of consciousness—psychology—and above all to the science of the phenomena of abnormal mental life—psychopathology. The medical sciences can never furnish the key to the book. Once psychology and psychopathology yield the key, the medical sciences have great value, the analysis of the form of the letters, the ink, the paper, yield a meaning and have a purpose.

A curious division has arisen between the practical fields of nervous diseases and mental diseases, a split that has created a very unfortunate and artificial gap in scientific

research. However important it may be from a practical standpoint to separate nervous diseases, that do not interfere seriously with the intelligence from mental diseases that require a radically different treatment, the division in the scientific investigation of the two sets of diseases has been a distinct drawback in the progress of knowledge of each. The progress of knowledge of mental maladies has suffered the most in being considered a field of investigation apart from that of the nervous diseases. The damage in nervous diseases involves the lower and more simply constructed parts of the nervous system, and were the understanding of these simpler conditions applied to the domain of mental diseases, greater advances would have resulted. One distinct aim of the Institute in many of its departments is *to bridge over this artificial hiatus in scientific study between nervous and mental diseases.*

Now we find that the nervous system (even in its highest spheres) behaves like other parts of the body in the presence of disease processes. It was suggested in the preceding section, that the nerve cell may exercise a protective agency against hurtful stimuli by retracting its arms, which also provided a period of rest for the cell to recuperate pathological expenditures of energy from its food supply. When the hurtful stimulus becomes more intense, as in the case of poisons coming in contact with the nerve cell, notwithstanding the higher organization of the neuron, it behaves just like its humbler associates in the liver, kidney and elsewhere. It may undergo changes in its internal organization in contact with the poisons of disease; its food supply may also be interfered with. We then perceive, under the microscope, signs of degeneration of the nerve cell as witnessed in other parts of the body, when their cells are exposed to the influence of poisons.

But even under the influence of poisons, the nerve cell has a wonderful degree of vitality and a large capacity for restitution, when the disease-inducing poisons are withdrawn.

It is a very important view to consider that the brain behaves like other parts of the body in disease processes. Guided by this view we can avoid the pitfalls of error into which those investigators are apt to stumble, who are prone to think that the brain has its own disease processes radically different from those of the body in general. In studying the changes in diseases of the nervous system one must always hold fast to one fundamental truth, that the brain in disease must not be regarded as something apart from the rest of the body, and must not be isolated as an organ *sui generis* having inaccessible mechanisms and mysterious powers.

Whether in health or disease the nerve cells are like other cells only more highly organized. They must obey the laws of cell life in general. For it must always be borne in mind that even the highest constellations of the brain are not composed of elements distinct from the humblest parts of the nervous system, not even different from the simplest nerve that pursues its pathway anywhere in the body. The fundamental structure of the constituent elements is the same everywhere whether in a simple nerve trunk or in the noblest and highest regions of the brain itself.

Enough has been said, perhaps, to indicate the very comprehensive character of pathological research at the present day, and the fact has been emphasized that patho-anatomical process in the nervous system, and above all the brain should always be considered in the light of analogy of the general patho-anatomical occurring through the body at large.

The study of patho-anatomical processes in the nervous system then, in this Institute, must always be guided by a most comprehensive knowledge of these same processes occurring throughout the whole body. It is, however, extremely difficult for any one individual to have a working knowledge of the morphology of disease processes in the body in general, and at the same time know enough of the nervous system to extend into this field the broad conceptions of *general* pathological research.

The application of pathological anatomy to psychiatric research is liable to be shorn of its full value. The opinion seems to be held that a single individual can command the whole sweep of pathology in centres for psychiatric research. The idea still hangs on that patho-anatomical research in psychiatry is to be given over to the specialized pathological anatomy of the nervous system. As a matter of fact the whole field of pathological anatomy is needed. In centres of psychiatric research then, it is best to provide for a co-ordination of the several fields of pathological anatomy by two or three workers in this branch who can pursue the several subdivided special lines of investigation and yet correlate them in order not to lose track of the generalized influences of pathological anatomy as a whole.

Taking our own institution* as an example, we may say that the department of pathological anatomy is somewhat at a disadvantage in not having a sufficient working force to cover the whole field. We have, practically, but one associate to take charge of the manifold bearings of this branch of the investigation of mental and nervous diseases and of its interrelation with other departments in the Institute. Another representative is needed in

* For details of the status of working force in Department of Pathology and division of labor in this field, see original report.

this field of study, especially in collaborating and extending the work among the members of the staffs of the hospitals, for most of our colleagues in the hospital *choose pathological anatomy as their favorite work.*

This insufficiency of working force in the department of pathology, has also been a very serious drawback in the acquisition of that particularly valuable kind of material for investigation which is not to be found within the asylum. The opportunity for acquiring this material, so valuable in the investigation of insanity, largely determined the seat of the Institute in the great metropolitan city of the State. This material is derived from autopsies on cases in which the nervous system is damaged by the great host of general bodily illnesses. The making of autopsies; the acquisition of autopsy material of nervous diseases; the preservation of this material with the requisite great care and detail, all involve an enormous amount of work, and we have been unable to take full advantage of the very opportunity, which led to the inauguration of the Pathological Institute in New York city, namely, the acquisition of material and facilities for the study of the first stages of insanity, the importance of which was emphasized in the introductory paragraphs of this paper.

Finally, let us be quite clear as to the distinction between pathological anatomy and pathology, a distinction which, unfortunately, is too often lost sight of. Pathological anatomy is concerned with the study of the structural changes associated with disease process. Pathology is the study of the disease process itself. Cell changes or other structural lesions are effects, traces of the process of disease. Pathology has for its province the study of the phenomena, the manifestations of the abnormal

function in disease. Pathology is a study of the *dynamics* of disease, whereas pathological anatomy is an investigation of its *statics*. In studying disease we should not be content to stop with making observations of pathological structure. This is but a small part of the problem. We should endeavor to go beyond this and explain the facts from a consideration of abnormal function. Pathology is the guide of pathological anatomy. Pathology, however, to be a trustworthy mentor of morbid anatomy, should be inspired by general physiology, the science of the general laws of the physics of function.

The comparison of the work of the earlier morbid anatomist to the inspection of the fireworks the morning after the show is still quite true to-day. The patho-anatomist of the present day is not far from the same position. In the contrast of the great progress of his deeper powers of analysis with the crude methods of his predecessor, the pathological anatomist of the present time is, I think, too prone to think that the force of Holmes' epigram has lapsed. In connection with the enormous amount of work rather heedlessly running into the channel of morbid structural changes it is quite as forcible as ever, and it will remain so as long as the study of morbid structure piles up its facts in delirious haste with too little reflection that only through the study of abnormal function can these observations have any broad interpretation. I mean by the study of abnormal function, not only the abnormal function of particular organs, but also the general principles of function in terms of cell energy, the province of *general physiology*. Pathological anatomy should turn to pathology, and this latter science to general physiology for the intrepretation of the structural changes in disease.

The same old problem, as to the cause and *modus*

operandi of the lesions, is still before the patho-anatomist of the present day. He has approached a little nearer to its solution, that is all. Like his predecessor, he still comes around after the show is over. The only difference between the two is that at present the inspection of what is left of the fireworks is much more extensive and penetrating. The patho-anatomist has passed from the observation of topographical lesions in organs and tissues to the minutiæ of cytological changes. Even so, the display is over. The living phenomena are gone and with them the key of explaining the meaning of the structural changes. This consists in expressing the structural changes in terms of function, of dynamics. Only the results, side products, impresses of the active phenomena of abnormal function are witnessed under the microscope. The observation of the finest minutiæ in cell structure is a long way off from the explanation of the energy process accompanying or rather giving rise to the cytolytic lesions.

Since the brilliant discoveries of bacteria and their toxines, and with the progress of seeking autogenous substances, the patho-anatomist of the day may be lead more than ever to think that the application of Holmes' epigram is a thing of the past. The difficulties of explaining the nature of pathological metabolism lie before us not behind us. The bacteriologist and the physiological chemist share honors in pointing out their discoveries as the causes of disease. The pathological anatomist points to the changes in cell, or organ, or tissue, when these causes are introduced into the body. It would appear, then, that the work of all three explained the *modus operandi* of the phenomena of disease. From the labors of the bacteriologist and physiological chemist, it would seem as if we had on the one hand the causes, and the

other hand, in the observations of the anatomist, the effects. The causes, however, are not the true essential cause; they are only proximate causes; and the effects are only a part of the operation of the true cause. The things which the bacteriologist and physiological chemist have found, although discoveries of brilliant importance in practical utility, are merely what touches off the fireworks; what sets free the pyrotechnic display. These bacteria and toxines, while greatly advancing our knowledge of the nature of disease, are merely sparks, as it were, which ignite the fireworks. Hence, these three scientists are rather prone to fall in with the idea that each particular disease corresponds to a particular set of fireworks, which can only be ignited by a particular kind of a spark. This is an extremely shortsighted view of the problem. A knowledge of the igniting impulse or a study of the remains of the fireworks or both combined, do not explain the process of combustion.

Because his two co-workers have discovered the agencies which set the fireworks free, the patho-anatomist must not lose sight of the fact that he is still inspecting the fireworks after the show is over. *The man who actually witnesses the display is the physician, the clinician*, but even he, on reflection, will confess that his methods are not searching and that he perceives only a small part of the process and its manifestations. In fact what is needed is the wand of the science of general physiology to guide pathological anatomy, bacteriology and physiological chemistry. *The great science of life in disease and health is general physiology, the science of function.* There is no need of qualifying physiology in its application to the study of abnormal function. For function in general is the central province of general physiology. The duty of

this science is to formulate function in terms of energy. When general physiology enters more extensively into the study of disease we shall see that the process of disease is one of mutations of cell energy and realize more fully the deep meaning which is conveyed by Sach's substitute in the term *energid* for the rather meaningless word—cell.

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Chapter X.

PATHOLOGICAL PHYSIOLOGY.

I have endeavored to show in some of the preceding sections that in these days of great specialization and subdivisions of the fields of pathological research, it is out of the question for any individual to have the capacity to cover the entire territory. Twenty, perhaps even ten years ago, when methods of investigation in pathological research were in a comparatively elementary stage of development and were used uniformly for the investigation of disease processes in all parts of the body, a single individual mastered the whole territory and was a general practitioner and pathologist to boot. He could observe symptoms during the patient's life, bridge over the chasm of death, as it were, and write the sequel of the story of the disease by observing the changes in the organs under the microscope. At the present time, the problems of

pathological research have grown vastly more complex The examination of different constituents of the body forms distinct and specialized territories of research, each having particular and intricate methods adapted for its special purpose, which cannot be used uniformly for the investigation of all parts of the body. Thus the changes in the blood alone, associated with disease, constitute a distinct field of research with specialized methods of investigation, and within the past few years an extensive literature has grown up emphasizing the importance of specialized micro-chemical investigation of the blood.

The study of the general changes linked with disease processes throughout the body at large, including the study of tumors, constitutes a very wide field of research, and is more or less subdivided into distinct branches of investigation. The study of morbid processes in the nervous system constitutes another field of pathological research, which is in turn subdivided into many specialized branches of investigation. The investigator who would explore this field must first traverse the domain of general pathological anatomy, must then learn the intricate architecture, construction and function of the nervous system, in order to apply to it his knowledge of the general nature of disease processes.

Pathological physiology in its turn constitutes a highly important and specialized domain of pathological investigation. Studies in this field of research that seek to investigate pathological function on a basis of physiology and induce disease processes experimentally require special skill in conducting operations on animals, and of watching the abnormal physiological manifestations of the animal after the experiment has been performed. It can be seen then that this territory merges over into that of

physiology. If pathology be restricted to the mere observation of *changes in form* within the organs and their constituent cells during the processes of disease, its power of investigation terminates quite abruptly in very many directions; in fact it almost loses its whole dignity and philosophy as a science. Most pathological laboratories are not laboratories of pathology, but of pathological anatomy. We must not only observe the alterations in form and structure within the cells during disease processes, but also interpret structural changes by the study of the changes in the *functions* of the organs and of the cells themselves. In brief, pathological physiology takes into account the *abnormal physiology* of organs and cells when exposed to environment simulating that of disease. This most important branch of research in pathology, respecting the abnormal physiology of the organism during disease, is best conducted from the standpoint of general physiology, and should make constant use of the methods of experimental pathology. Pathological physiology fills up the gaps in the knowledge of disease processes gained by studying them in the human subject alone. These gaps are indeed wide and deep.

Anatomy deals with the structure of the normal organism. Physiology is the science of function.

Each of these two great sciences of life is specialized on various provinces, which need not be considered here except as relating to the divisions made in the study of disease. Both of these sciences become subdivided into specialized fields of inquiry depending upon the normal or diseased condition of the organism. Thus we speak of normal anatomy and histology as the branches which investigate the structure of the normal organism. Similarly normal physiology is used to designate the study of

normal function. Pathological anatomy and histology investigate the structural changes concomitant with the process of disease. Pathology is the study of function in disease, and is, therefore, really identical with physiology. Pathology is an application of general physiology to the investigation of changes of function in disease. Pathology, however, is so often confused with pathological anatomy that it seems well to emphasize the fact that the great and guiding study of disease is not one of structure, but of function. The investigation of the disease process is not pathological anatomy, it is a physiological study and has a higher dignity as a science than morbid anatomy. In fact pathology should be the guiding science for pathological anatomy. In order to bring into greater prominence the necessity of physiological methods of investigation into the province of the study of disease, we have, therefore, used the term pathological physiology—the physiology of disease. Throughout this chapter the application of pathological physiology has been given a rather specialized character in being limited to the study of abnormal functions of particular organs in disease, both in the human subject and by experimental work on animals. In the future, after this department becomes established and grows, we shall endeavor to have its work guided by the broad principles of comparative or general physiology—the study of function in general on the energy basis of life phenomena. We should remember that the process in disease is not different in nature from the processes of normal life. In disease normal physiological processes take on a wider range. Cycles of cell energy liberation and restitution in disease are not different from the cycles in normal life. The range of the oscillations of the cycles are merely wider.

If the normal physiologist would have a flood of light shed upon normal function of cells and organs he should study the process of disease. *It is only through a study of the abnormal, the pathological, that we can hope to understand the normal.* This fact is not sufficiently understood by the devotees of the various normal "*ologies*."

As normal physiology deals with the functions of the different tissues or organs in the normal organism, pathological physiology investigates the abnormal functions in the diseased organism. But the questions which pathological physiology has to decide are much more complicated than in those of normal physiology, because of the protean aspects of disease and the great variety of phases of the pathological process. Disease is very seldom so simple a phenomenon as the expression of the abnormal functioning of a single organ of the body. The body is a united whole, and the various organs are so indissolubly interrelated that abnormality of functioning in one organ may produce a widespread effect on the functions of the other organs. Disease is a complex whole of abnormal functions of various organs, although primarily it may result from the departure of a single organ or tissue from its normal functions, chemistry, and structure. In disease the pathological physiologist is, as a rule, confronted with a whole complex group of abnormal functions of several organs, and he has to sort out and differentiate how far the abnormal functions of each organ contribute to the general symptomatology and to discuss the interrelation of the abnormal functions of the several organs.

Before long he should, from the general biological study of function, discuss the functions of diseased organs in terms of cell energy. This will give the key to the explanation of the morphological changes in disease.

We must not be carried away by the fairly widespread example of centering pretty much the whole of scientific inquiry of medicine about the microscope, the crucible and the culture tube. Let us keep in mind that clinical work, the study of the *living phenomena*, the strict scientific investigation of psychomotor manifestations, is just as much a great department of scientific research as those laboratory investigations in pathological anatomy, bacteriology and physiological chemistry. In fact, I think that the study of the living phenomena is far more important than the other studies, for the simple reason that only through the study of the living phenomena of disease can we arrive at broad, guiding principles to direct and interpret the work of the laboratory sciences. The study of the living phenomena then, far from being put in the background of medical science by laboratory workers should stand foremost; it forms the mentor and the guide of these other sciences.

Clinical investigations conducted on the strict basis of general physiology and psychopathology give a basis for deductive reasoning, for scientific co-ordination of the scattered facts of the laboratory sciences. The clinician, fortified by the great principles of general physiology, pathology and psychopathology, armed by the methods of scientific observation and experimentation stands close to the highest plane in medical science—the observation of living phenomena, the manifestations of disease. At present, however, the methods of the clinician fall short of this standard—they are not wholly adequate and searching. A whole host of phenomena slip out of his grasp or are but dimly perceived by him. Physiology, functional pathology and psychopathology possess the methods of studying the living phenomena accurately and compre-

hensively. By pathological physiology, functional pathology or simply pathology, I mean to indicate the study of life activity in disease by the methods of a science which considers such phenomena as manifestations of *energy*. Clinical research, based on the principles of pathological physiology, ought to take precedence over the other medical sciences, such as pathological anatomy, bacteriology and physiological chemistry, and to lead them in *thought*. The study of function in terms of energy *states the problems* which are to be verified by the statical sciences. Through the leadership of physiology dealing with the ultimate cause, energy, the scattered, disjointed facts of pathological anatomy, physiological chemistry and bacteriology will become scientifically useful and yield material that can be used for *theory*, *generalizations*, *laws*—the ultimate aim of scientific research.

Inasmuch as we are largely debarred from controlling diseased human beings for the application of physiological methods of inquiry, we must obviate these difficulties by inducing morbid function in animals. This will not invalidate at all the soundness of the *general principles* of the *modus operandi* of abnormal function. These general principles (the nature of excessive ranges of cycles of cell energy liberation and restitution, and the nature of stress or resistance of latent cell energy to stress removing impacts) we should determine first through comparative or general physiology. We shall then be in a better position to reason from these generalities respecting cell energy as to the nature of functions of cell communities in the particular organs and tissues. General physiology of disease comes first; special physiology of diseased organs should be pursued in the light of the former study.

Observation at the bedside is, to a large extent, a practical application of pathological physiology, but in most instances, such observation can only state the substance of the question as to the nature of disease processes, namely, the origin, cause and course of the disease, and is seldom able to answer it. Pathological anatomy may demonstrate that a given disease is followed by certain lesions in certain parts or organs of the individual, and may further show that the same lesions are always associated with the same disease, thereby making a certain relation between the two factors quite probable. But in order to change probability into certainty other methods of investigation are requisite. It is necessary to reproduce the disease experimentally and artificially in animals. If the pathological lesions found in a given disease can be initiated experimentally in an entirely healthy organism and disturbances in the functions of the organs similar to those of the disease result, the chain of evidence demonstrating the association of the symptoms and lesions is complete. This plan is one of the great aims of pathological physiology. Its highest motive is the interpretation of symptoms, abnormal function, in terms of cell energy. The greatest guide to the study of cell energy is the investigation of neuron energy. This is the key.

In this experimental method, not only in pathology but in all biological and natural sciences generally, lies the great power and advantage of modern methods of investigation over the old lines of research. In some instances, the experimental method in the study of disease may be applied to human beings, more particularly in methods of treatment. In fact, all of our present knowledge of the action of drugs has been gained

through experiments in pathological physiology. In fever, for instance, the modifications induced in the abnormal functions of the body by antipyretics or a cold bath are useful applications of the experimental method in pathological physiology.

The opportunities for using experiment in abnormal physiological manifestations of human beings in disease are seldom afforded. Hence we have to make use of experiments on animals and compare the results with the phenomena of morbid processes in man. It may be said that pathological processes induced in animals cannot be compared with those occurring in human beings, for the organization of each is different. This is certainly true to some extent. There are, for instance, pathological processes of the gravest import to human beings, which, as yet, we have not succeeded in reproducing in animals, such as tumors, syphilis, epilepsy, the small-pox group, etc., and many diseases of the nervous system. There are again certain factors vaguely grouped under the terms predisposition and immunity which make an individual of the human species prone to a disease process and shield an animal from the same process, and *vice versa*. The idiosyncrasies of man to many diseases from which animals seem shielded go to show how much we still have to learn of predisposition, immunity, and the factors of heredity and vulnerability in disease. These facts in themselves, on the other hand, emphasize all the more the imperative necessity of the more extensive application of the experimental method in pathology, for the diseases which seem beyond the reach of the experimental method were formerly and are now precisely the very ones the explanation of which is most obscure and unsatisfactory. In many instances,

fortunately, one is quite justified in considering the abnormal functions of the organ in an animal, when a given disease process is induced experimentally, as equivalent to the abnormal functions in a human being in that disease.

The cardinal functions of the corresponding organs are the same in all animals with higher organization, and the structure of these organs resemble each other very closely. If, then, having produced in an animal the same lesions corresponding to the ones found in the human subject, the animal is found to manifest the corresponding set of symptoms, the causal relations of the abnormal functions to the structural change rest upon a firm basis. This is the way that the brilliant and practical results of bacteriology have been achieved. Without the use of experimental pathology, bacteriology would indeed have been a sterile science in the practical domains of medicine. It would have resulted in a piling of Pelion on Ossa of mere facts of the life-history of bacteria, and their all-important pathogenic qualities would have remained comparatively unexplored.

We should not strive always to experiment on animals which, by the high and complicated development of their organization, are more or less related to human beings, but, on the contrary, greater extension of the experimental method in pathology should be made on the lower animals where the brilliant work of Metchnikoff has given the key to the explanation of the phenomena of inflammation. The less complicated the organization of the animal, the less complicated are its specific functions, and the easier it is to comprehend its structure and functions in either health or disease. But this field, experimental pathology in the lower animals, belongs to or

is shared with the province of cellular biology and has already been alluded to. From these studies it will then not be difficult to progress to the understanding of the aspects of disease in more complicated organisms. For our purposes, experiments to produce disease processes on the more *highly organized animals*, belong more properly to the territory of pathological physiology. For the study of the specific functions of various organs a distinction between higher and lower realms of animal life is perhaps on practical grounds admissible; because the cellular biologist is more familiar with the lower forms of life than the special physiologist (medical physiology, physiology of man). From the standpoint of the general study of function, from the point of view of general physiology, such a distinction is wholly arbitrary and illogical.

When morbid processes are induced experimentally in animals, to find the equivalence of disease in the human subject, the services of physiological chemistry, bacteriology, and pathological anatomy, must be called upon; the secretions and excretions must be examined; the physical methods of examination used in the clinic or laboratory of normal physiology must also be taken into account. In addition, the tissues of the animal are to be examined by the microscope after death. To a casual observer, it might seem then that pathological physiology, having no methods of its own, could hardly be called an independent branch of medical science. This is as little true of pathological as of normal physiology. The aims of pathological physiology, the questions it has to study and decide upon are peculiar to this particular science, notwithstanding the fact that it works largely with methods of research used in other branches of medicine. Pathological physiology has a method of its own, namely,

animal experimentation conducted along certain lines peculiar to this branch of science.

Like every other branch of medicine, experimental pathology or pathological physiology is closely, even organically, related with the other branches. It is a *connecting link* between *pathological anatomy*, *physiology*, *bacteriology* and *physiological chemistry* on the one hand, and *clinical medicine* and *hygiene* on the other. Its work is indispensable, not only for the progress in the treatment of disease, but also for advances in the highest art of medicine—the prevention of disease. Its greatest province is to guide the work of pathological anatomy, bacteriology and physiological chemistry, and furnish the standpoint for explanation of this work. Progress in modern surgery, in serum therapy, in the prevention of epidemics, in immunization, public hygiene and antisepsis owes a great debt to experimental pathology.

The study of the pathology of the nervous system is more dependent upon pathological physiology than that of any other system in the organism. All the other organs of the body differ from each other by anatomical structure and by function, while different parts of the central and peripheral nervous system have the same anatomical structure and still their functions are entirely different. We can hardly see, for instance, any morphological or chemical difference between some parts of the brain, the irritation of which produces contractions of the muscles; or other parts of the brain, the irritation of which produces contractions of the circulatory system, rise of temperature of the body, and so on.

The fact that every part of the brain has only to perform a certain part of work in the physiological division of labor in the nervous system, was shown first

by Hitzig and Fritsch by the aid of animal experimentation. They irritated certain places in the convolutions of the brain with an electric current and always received contractions in certain muscles. These experiments having such a great theoretical importance for the understanding of physiology of the brain, played even a more important part in the pathology and in the localization of functions of different parts of the nervous system.

These experiments enabled the physicians to find in a living man a tumor of the brain, and the surgeon to direct the knife to its location with almost mathematical accuracy. Experiments of this kind corroborated the differentiation between focal and essential epilepsy, and it is to be hoped that the day is not far distant when the simulacrum of epilepsy may be artificially induced in animals through the labors of experimental pathology. If the simulacra of epileptic phenomena could be experimentally and permanently induced in animals, it would furnish the key to the explanation of this obscure process. All the facts which the pathological anatomist and physiological chemist have gained in the study of this dire malady give no explanation of the *process* that gives rise to the epileptic phenomena.

Animal experimentation has also proven that extirpation of certain portions of the cortical part of the brain always produces a degeneration in the same nervous fibres, proving thereby the neuron theory and showing the location and topographical distribution of different groups of functionally related neurons. Many more examples could be added, showing the value of pathological physiology for the study of the nervous system.

Far from being fit to investigate the phenomena of

consciousness, morphology and chemistry alone are not, and never will be, able to explain all the phases in the *function* of the nervous system, not only because we are unable to differentiate morphologically or chemically one pathological process in the brain cell from another, but also because the same pathological process of two different parts of the brain, if their functions are different, can have a different influence upon the organism as a whole. It is, therefore, not sufficient to study the morphological and chemical changes of the nervous system in its pathological state. We must also see what influence such a diseased nervous system has upon the different systems of the organism, such as the action of the heart, the blood pressure, the respiration, the general metabolism, and so on, as these all depend upon the nervous system, and must be changed when the latter is changed. Conversely the effects of changes in circulation, respiration, general metabolism and changes in organic and vegetative somatic functions upon the higher parts of the nervous system must also be taken into account. This latter topic must be studied by the pathological physiologist and psychopathologist conjointly.

We can illustrate our point best by the plan of studying the influence of drugs or poisons on the nervous system. Let us suppose that we introduce into an animal certain drugs that produce convulsions or sleep; no matter whether we find morphological or chemical changes in the nervous system or not, we will not know thoroughly the nature of the action of these drugs until we examine, by all the physical and physiological methods at our command, the influence of the drugs upon the nervous system itself and all other systems of the body, the action of which is regulated by and depends upon the nervous system.

From one particular standpoint, however, this branch of research deserves special emphasis, for it relates to some questions of ultimate and practical importance regarding the insane. One of the specific *rôles* of pathological physiology, in psychiatric and neurological research, lies in the *determination of the action of drugs upon the nervous system*, and above all the brain. It must be confessed, that in the treatment of the insane, our knowledge of the effects of drugs upon the metabolism of the nerve cells is very obscure. No one will deny that it is of the utmost importance to know what we are doing to the nerve cells in administering drugs to the insane. At present the knowledge of the action of the drugs given to the insane, is known simply by the general physiological effects, and not by the chemical reaction between the constituents of the nerve cell and the drug itself. Our knowledge of the action of drugs on the nervous system is empirical to the last degree. In epilepsy, for instance, I do not hesitate to say that in very many cases the administration of bromides on this entirely empirical basis, although relieving the symptoms, may actually in the course of time damage the nervous system severely. The bromides, if given continuously, may constitute an actual poison to the nerve cells, and in this disease one evil may be added to another, in that the ravages of the disease process of epilepsy is augmented by poisoning the nerve cells by a drug, whose action upon the delicate organization of the nerve cell is altogether unknown.

Epilepsy seems to be due to the action of some stimulus, which though mild in intensity, may, by its persistence, act in the higher spheres of the brain. This stimulus may come from a variety of places in the body. It may arise from the intestines in the form of a mild poison, which

may escape into the blood from some departure in the complicated chemical operations attending digestion; it may travel up one of the many nerves of the body from some irritation which involves the ends of these nerves; it may be due to the irritation of a tiny splinter of bone pressing on the brain after a blow upon the head, etc. In an individual of inherent instability of the higher spheres of the brain, this constant stimulus finally causes a sudden dissociation of this part of the brain from the lower spheres beneath, by means of the retraction of the tentacles of the nerve cells. These nerve cells in the upper spheres of the brain become fatigued, through the constant reception of the stimulus, and retract their arms to avoid the noxious and offending impulse. But in the sudden retraction of the upper spheres of the brain, which grasp and control the lower portions, the energy of the latter is suddenly unbridled and loosened, and the epileptic fit results. Now it is quite probable that in deadening and benumbing these upper spheres of the brain by the use of bromides, so that they no longer exhibit a sense of fatigue to the stimulus much harm is being done. It is quite true, that the symptoms of epilepsy may be controlled in this way, but are we not poisoning the nervous system to gain this end? It were far better to ascertain the cause of the epileptic fit—the persistent stimulus coming from some distant place in the body—and attempt to remove this, rather than to injure still further the highest spheres of the brain, by benumbing with a poison their sense of fatigue.

If the large and continuous amounts of bromides be given to animals, as has been determined in some research work in one of the State hospitals, the result is the poisoning of the nerve cells manifested by the phenomena of

degeneration. While the drug is not given in epilepsy in such poisonous amounts as in these animals, nevertheless it must act in the same way, though to a less degree. If a perfectly sane man were continuously dosed with bromides, it would seem almost certain that in the course of time he would begin to show a dissolution of the higher spheres of the brain, whose activities are concomitant with the manifestations of the highest forms of mental operations. It must appear, then, from this single example, how important it is to know the action upon the nerve cell of these drugs. Hence I would enter a plea for provisions in pathological physiology at this Institute, the more so as I have already mapped out an extensive series of experimental researches to determine the action on the nerve cell of the drugs used in the treatment of insanity.

In addition to the determination of this important and practical question by this department, many problems relating to self-poisoning in the body fall within its scope. Subtle disorders of a whole system of organs within the body whose duty is to maintain the blood in a proper equilibrium, may induce a poisoning of the nervous system with grave results. A very large share of our knowledge of diseases that spring from disorders of the organs producing the blood and maintaining its chemical and morphological equilibrium has been derived from the researches of pathological physiology. A large share of work still remains to be done in this field, and facilities for the experimental study of the relation of changes in these blood-producing organs, to poisoning of the nervous system in mental and nervous diseases, ought to be provided for at this Institute.

We have no one on the staff at present who has the requisite time or specialized training to undertake work in

the field of pathological physiology. An associate in this department should be able, in addition to his own special investigations, to perform all the operations on animals desired by the other associates in the course of their researches, or to devise new operations and experiments as may be necessary in the course of psychopathological, pathological, bacteriological or chemico-physiological investigations. In addition to this, he should conduct all the physical and physiological parts of the examination, transfer and apportion the morphological, chemical and bacteriological material to their respective departments for detailed investigation after the experiment has terminated.

Chapter XI.

THE INVESTIGATION OF BLOOD IN INSANITY.

The investigation of the blood in insanity derives its importance as a distinct field of research, from the fact that this is the medium of conducting the food supply to the nerve cell. When the nerve cell works, it expends energy, and the elaboration of energy is carried on within the body of the nerve cells from crude food materials derived from the blood vessels. The theory has lately become more and more substantially founded upon facts and observations, that not an inconsiderable share of mental and nervous diseases are due to the actions of poisons upon the nerve cell. These poisons, which comprise a very large group, are sometimes bred within the interior of the body; they are often derived from bacteria and frequently taken into the body from extrinsic sources.

There is, however, great danger of carrying this explanation of the action of poisonous substances upon the

nervous system, too far, and thereby underestimating the *equally important factors of deficient food supply and pathological fatigue of the nerve cell in the production of nervous and mental diseases.* In observing the actions of poisonous reagents upon the nerve cells, the concomitant impairment of *their food supply in relation to the work they perform* must also be jointly taken into account, particularly where the poisons, although mild in intensity, are of a dangerous character from their persistence and chronic action.

Investigations of the blood in the living patient, then, are of paramount importance, because *in changes in the blood we have a barometer, so to speak, of the fall or adulteration of the food supply of the nerve cells.* We have not only to consider the specific action of poisons upon the nerve cell, but the secondary factor of the interference and adulteration of food supply of the nerve cell which this poison causes by circulating in the blood. In one of the commonest forms of insanity—general paresis—constituting a considerable per cent of the patients in the hospitals near the large cities, the cause of the disease seems to be a slow, gradual, unrelenting process of diminution of the food supply brought by the blood, thus inducing starvation of the nerve cells.

The investigation of the blood in insanity has proved of such practical importance as to enable one to base on it therapeutic measures and to indicate the percentage of cases that may be benefited by a particular line of treatment. Herein is certainly a practical application of the value of investigation of the blood of the insane. If there be one factor more important than any other in the production of mental and nervous diseases, with the exception of toxic agents, it is the *quantitative* and *quali-*

*ficative impairment of the food supply carried in the blood vessels to the nerve cell.**

Much important work remains to be done in establishing more definitely the factor of impairment of food supply to the nerve cell in relation to the genesis of mental and nervous diseases, and the Pathological Institute of the New York State Hospitals can ill afford to neglect this branch of research, not having the aid of an associate in pathological physiology.

This once more may serve as a good example to show the inefficiency of the working force of the department of pathology, in having only one associate. Pathological research work covers so many specialized fields of inquiry that a staff of at least three associates is required. I think, however, that both pathological physiology and the investigation of the blood of the insane may be carried on by a single investigator.

To sum up, it is advisable, if not indispensable, that three sub-branches should be provided for pathological research in the investigation of the insane, each under the charge of a single associate. These sub-divisions are:

I. General pathological anatomy.

II. Special pathological anatomy of the nervous system.

III. Pathological physiology, including the pathological histology of the blood.

* Some of these details respecting the significance of the excretion of the metaplasm granules from the nerve cell in relation to deficient food supply and pathological expenditures of energy are worked out in my paper "The Toxic Basis of Neural Diseases," now in press for a future number of the ARCHIVES OF NEUROLOGY AND PSYCHOPATHOLOGY.

Chapter XII.

ANTHROPOLOGY.

The importance of heredity as a factor in the production of insanity has been hinted at several times in this text. In the previous section on cellular biology, attention was drawn to the fact that the advances in that science had set forth a working hypothesis for the physical basis of heredity; that the cell scientist had been able to select a certain element in the egg cell which in its fecundation was mingled with an equal amount of the same element from the sperm cell; that these two paternal and maternal contributions to the beginnings of the new being were intimately wrought together and distributed in equal amounts in the process of cell division to every individual cell in the whole organism of the new individual. Hence the new being bears the stamp of the characteristics of both parents.

The facts of the relation of heredity to insanity are to be interpreted only by applying to them the remarkable advances of cellular biology into the nature of the germ plasm and the investigation of variations in general through the study of evolution. The whole essence of the problem of heredity in insanity lies in a thorough appreciation of these researches of the germ plasm and of the nature of variations, and the psychiatrist who does not familiarize himself with these investigations in the community of biological sciences can hardly expect to gain any clear insight into the factor of heredity in insanity. The discussions of this subject frequently carried on with but vague and hazy recognition of the present status of cellular and other biological researches into the physical basis of heredity bears testimony to the isolation

of psychiatry from all other branches of science. Psychiatry is its own worst enemy in not stepping forth and affiliating with the biological and medical group of sciences.

Changes in the germ plasm from either the paternal or maternal side or both, operate most powerfully to determine the weal or woe of the progeny, according to whether the nervous system grows up from normal germ plasm full, sound and stable, or contains as a result of pathological germ plasm some hidden, subtle, instability of the highest, most delicately organized and precious upper centres of the nervous system, endowed with the highest intellectual attainments and control over the brutal, credulous, immoral and aggressive sub-conscious self.

What are the agencies which damage the germ plasm and cause departures from its normal constitution? Precisely the same agencies, to a certain extent, which cause degenerations or induce disease processes in other cells of the body besides the germ cell. It is not a transmission of acquired characteristics. The germ cells are damaged principally by the same agencies as produce the variation and not necessarily or, only to a slight extent, the operation of the variations themselves. These agencies may be summed up under poisons and factors which depreciate the food supply of the body cells.

While in their whole life-history the germ cells are supposed to be set apart from the rest of the body cells for the distinct and sole office of continuously propagating the species, it is not possible for nature to colonize them so completely as to shield the germ cells from the damage inflicted by poisons or deficient food supply. Thus, for example, the poison of syphilis and the chronic and

persistent poisoning of the body by alcohol, both of which seem to operate largely by diminishing quantitatively or qualitatively the food supply of the body cells, not only cause degeneration of the nerve cells, but damage the germ cell simultaneously and during the growth of the embryo inflict other ontogenetic variations also. This is the reason that the progeny of parents whose nervous systems are poisoned by alcohol and syphilis is notoriously defective in the weak organization of the superlative and most intellectually endowed spheres of the nervous system. For if a very slight defect or chemical change or a change in the configuration of atoms occur in the gigantically complex molecules, the germ plasm as a result of the action of these poisons, the effect in the next generation will crop out in the highest and most complexly organized parts of the body rather than in the more lowly organized and comparatively undifferentiated parts. This is why the nervous system, and above all, its most lofty portions, are found wanting in perfection when the germ plasm is in a pathological condition.

According to the degree of pathological changes in the germ plasm do the defects of development of the progeny pass successively from higher to lower and lower planes of organization in the nervous system so that all grades of degeneracy and mental instability may be witnessed down to the weak-minded, the imbeciles, and idiots. The exceedingly complex molecular constitution of the germ plasm and the complicated process of reduction or halving of the germ plasm in maturation of the egg and sperm cells in relation to the action of toxic agents and deficient cellular nourishment is of such urgent importance that we ought to try to devise plans for the department of cellular biology to approach the problem from the experimental

standpoint among invertebrates which afford good opportunity of applying toxic agents to the germ plasm.

During childhood such inherited incapacity of the energy of these higher parts of the nervous system does not always appear, unless the hereditary effects due to damage of the germ plasm or other ontogenetic variations be of a certain degree of intensity or persistence, for at this period such higher centres are comparatively little used. During adolescence and later life, however, when these higher centres of the nervous system are called upon for the greatest and most extensive expenditures of their nervous energy they may fail. We then perceive the outcropping of hereditary influences in a defective mechanism in the neuron to elaborate energy from its food supply. It becomes worse in the next generation, for the reason that this unstable brain energy in the first generation is liable to cause the individual to commit excesses; to set aside moral laws in decent, wholesome living, tamper with the nourishment of the body and introduce alcohol or other poisons into the circulation of the blood. Thus the germ cell in the second generation becomes still further degenerated in that it suffers from this exposure to poisons and imperfect food supply in the blood. Degeneration of the germ plasm in the second generation is liable to bring about pathological conditions in the nerve cells and other somatic cells disturbing the general metabolism of the body or inducing a craving for toxic substances (alcohol) in the third generation. This reacts upon the germ cells in the succeeding progeny and their degeneration is advanced in progressive generations. Degeneration of the germ plasm once established tends to set up a vicious circle increasing the degeneration in each successive progeny, unless somewhat mitigated by

crossing with undamaged germ plasm. The third generation of such a succession is liable to become quite unstable in the energy of the higher portions of the brain which hold the lower spheres in check. It is from this or succeeding generations* that are recruited the inmates of the prison, of the lunatic asylum, of the reformatory and of the hospital for the epiletic and idiot.

We are, however, in such a backward state of general knowledge of all these phenomena among the masses that we cannot mitigate these agencies (better control of syphilis) or seize the earlier phases of generation psychopathies in the beginning, where they ought to be taken in hand, but must wait for the end, so that the State has to spend millions taking care of sickly and incurable degenerates. Spontaneous variation and environment must, of course, be taken into consideration in the march of degeneracy. But from whatever sources or combinations of these sources the degenerate and the candidate for the prison and the asylum springs, we must identify him and have knowledge of him in the earlier stages of his pathway.

Now as to the use and purpose of anthropology. The relations of anthropology to medical science are somewhat vague. No one seems to define clearly and exactly just what anthropology is to do, or what results we may expect from it; consequently one may avoid the ponderous definitions usually given and attempt to explain in simple language the use of anthropology in the science of medicine. Anthropology, in relation to the medical sciences, is simply a convenient term to indicate that two or three sciences are made use of collectively to study not

* Vide consideration of liberation of energy throughout successive generations in the paper on Neuron Energy.

only individual cases, but also large bodies of men. In this way the science simply makes use of anatomy, physiology and psychology, more or less simultaneously, in investigating normal and abnormal phenomena of human life.

Now our object with anthropology is to conduct these anatomical, physiological and psychological investigations, to determine the characteristics of men with abnormal nervous systems as compared with the normal. We wish to identify the degenerate; we wish to learn departures in the physical and psychical characteristics of men at various stages along the pathway toward the prison and the asylum. At the asylum we already know fairly well what departures the insane show from the average normal man. In the asylum, however, only the last stages of mental and physical abnormalities preponderate, and we depend on anthropology to work out the initial and intermediate stages in the course of degeneracy.

The first stages in the history of the degenerate, in a great majority of cases, is some defect of the germ plasm, and this or other ontogenetic variations give rise to the stigmata or marks of degeneration, both mental and physical, found in many of the inmates of the prison, of the reformatory, of the hospital for the epileptic and for the insane. In determination of the mental characteristics of degeneracy, anthropological investigation must be under the guidance of psychology and psychopathology.

Undoubtedly one of the most resourceful fields of anthropological research in its bearing on abnormal mental life is the study of the psychopathic and neuropathic criminal. The larger part of the sphere of what is called criminal anthropology really belongs to pathological psychology, since this possesses the methods of analyzing the abnormal mental phenomena shown in a certain proportion

of criminals and can furnish the ideas, the philosophy of correlating the facts. The other side of the investigation in criminology, the determination of the physical abnormalties, belong properly to anthropology. A union of both lines of research would seek out both the psychomotor and physical departures in the criminal, their interrelation, and ultimately, laws and principles governing these variations.

By criminal anthropology we understand then a coalition of powers of research grasping at both the physical and psychical variations of the criminal in so far as his acts are symptoms of a defective organization or manifestations of pathological processes. Criminal anthropology, if I understand it aright, is the study of the *psychopathic* and *neuropathic** criminal. It is the study of those criminal classes only who are of a psychopathic or neuropathic nature.* This requires the combined work of psychology, psychopathology, anatomy and physiology. The sociological aspect concerns us very deeply in that it may furnish aid by contributing to some guiding principle of the research, but any specialized work along the lines of sociology lies outside of our sphere. Yet a co-ordinated study of the defective or diseased criminal ought to be productive of useful material for the sociologist to apply in his own especial problems.

It will be necessary from our standpoint to take a cursory glance at the development and aims of anthropological study (including above all the psychopathological investigation) of the diseased or defective criminal, for criminology has but comparatively few students. Students of this subject have a hard road to travel both as to the discouragingly difficult nature of the subject matter and

* See article "Neuron Energy."

the lack of encouragement and even the discredit they receive from other workers in science.

Possibly several things have combined to make criminal anthropology seem an unproductive or unattractive field of work. One reason for the lack of enthusiasm in the study of the criminal is that the science in itself is exceedingly young. It has barely had sufficient growth to establish ideals and plans of work. Consequently the study is somewhat vague in its outlines. It has not developed enough to map out pathways of investigation that others may follow with profit. Like many other branches of science dealing with life phenomena, general principles and working hypotheses are exceedingly difficult to ascertain by confining the research exclusively to the subject itself. It would be far better to study the pathological phenomena shown by some of the criminals where similar phenomena are greater in degree or are proceeding at a more obvious rate. One might then from such sources find some general theory, even if it be only provisional, to test the same in criminals and to see if the manifestations of the criminals are in accordance with the truths that have been learned about abnormal physical and mental variations elsewhere.

Another cause, perhaps, that has depressed the study is that among the laity especially, there is a feeling of distrust that the tendency of the advancing study of the criminal will be to ease him of responsibility and make crime attractive by making excuses for it under the guise of psychopathic maladies. In fact, the practical application of scientific analysis of criminal actions has often been abused in the halls of justice, and it is liable to be done often again in the future, as long as such evil systems of ascertaining scientific truths as that

of "expert testimony"* prevail. Still in the long run progress in the study of criminology cannot fail to right such evils and to call for a less backward attitude of the law to regard the scientific side of criminal acts.

One other reason that may be given to account for the spirit of indifference in relation to the study of criminal anthropology is that its exponents have worked with fallacious methods of research.

The study of the criminal, in so far as he is neuropathic or psychopathic, hinges largely on the questions of the laws of human inheritance and human variations both physical and psychical; and these are the most vexed questions of the day. Progress has advanced so far only as to state them and point out the direction of the inquiry rather than to make an attempt to answer them. These questions point conclusively to the fact that the study of the criminal must be guided by general biological and psychological standpoints.

The obstacles in ascertaining the laws of mental and physical variations in man by focussing the study on the psychopathic or neuropathic criminal are altogether too great. In a study surrounded by fewer complexities, the method would be to assemble the principal external facts and by rising from them through the resources of the methods of induction arrive at the laws. But in criminal anthropology the difficulties are too great and transcend the powers of this method. It will be necessary to go to many outside fields of research in general biology and psychology to arrive at some standpoint for the guide of the investigation of the criminal.

To carry on work with the methods of induction experiment is necessary. In working with these methods we pro-

*See Van Gieson and Sidis "Expert Testimony," STATE HOSPITALS BULLETIN, 1897.

ceed by noting certain external phenomena or effects and by successively varying the surrounding circumstances, eliminate irrevalent pertubations until, finally, we arrive at the essential interrelation and correlation of the phenomena, that is, we discover their laws. Two conditions are requisite in this method, first to vary, by experimentation, the conditions surrounding the phenomena, and secondly to observe the particulars or analyze the components of the phenomena after the experiment. In the investigation of the criminal classes it is very difficult to do either. In the inductive sciences we can control the phenomena and hence are able to experiment. In the study of the psychopathic and neuropathic criminal classes it is rather difficult to employ the experimental methods. The student may note a whole multitude of facts, but to assemble them in orderly fashion, to estimate the relation they bear to each other, and to harmonize the relation of their segregate and aggregate value with our accredited knowledge and most certain experiences of other physical, mental phenomena will indeed be a hard task. The observer stands in danger of becoming lost and hedged in in his own mass of facts. From this standpoint the study of the diseased members of the criminal classes might go almost indefinitely and do little more than wander about in the maze of its facts without finding an outlet, for in the concentration of observation in the field of the criminal alone, no foothold can be promised for reflection and inference from the facts. Criminal anthropology no more than psychiatry or any other life science can be isolated from other fields of knowledge. Otherwise it loses its philosophy and its dignity as a science, and the finest and most patient of observation fails to be effective without the guidance of and reciprocal impetus to theory.

Perceiving then the present narrow standpoint of criminal anthropology, what other recourses are open? It is a question well worth while to inquire into; for the most important thing is to have some definite standpoint from which to conduct the lines of the research instead of catching hold of facts wherever we can or in whatever order they come along. One must endeavor to see through the relations of things instead of blindly hitting upon these relations through one successful effort in a series of chances. If a man is to make ten or twenty thousand measurements of criminals and the like, he is indeed expending energy and conducting close observations, but he also ought to have formulated clearly in his mind beforehand the precise object of these results and what use they are in relation to our stock of knowledge of mental and physical variations in man gained in other directions. If such a set of measurements are undertaken to verify a theory established by a substantial number of facts in human and general morphology, or from the standpoint of general study of the laws of variation and inheritance, no fault is to be found. But, on the other hand, if the investigator does the work at a venture and says that he cannot predict what startling results may not come forth from the computations, and has no well defined object in view except that he expects to hit upon some generalization from these bald columns of figures, I feel that it is not a high form of scientific work. It seems a little like the method that people use in solving mechanical wire puzzles by adjusting and turning them over in the hands until some one of the random attempts succeeds.

Criminal anthropology is as yet in too early a stage of development to seize upon the phenomena of its special field directly by the inductive method. It must first have

theory, even if faulty, and make a little further progress on this basis in the marshalling of the facts. From this induction may be used then further deduction. By alternately passing from the one method to the other slow, gradual progress can be made. For this is the history of the first stage of growth of science in general. The facts lie before us all the time. But in the complexities surrounding the phenomena we are not able at first to unearth them and to have all at once perfected methods of inquiry to discover them. The most valuable facts lie beneath the surface and often defy the most ingenious methods of exploration. At the beginning, science has relatively few facts and these lie upon the surface and are obvious. Theories have to be invented and a *modus operandi* established for the succession of the phenomena from their antecedents and gradually the theories become more perfect.

To work out some guiding theories criminal anthropology needs the methods of deduction. In deduction we invent certain principles in the mind and descending upon the phenomena verify them to see if they agree with the hypothesis. In this way facts refractory to control and experiment, although yielding to observation, may be brought under the dominion of the hypothesis.

How can this deductive method be brought into play in criminal anthropology? We have two things to consider, the mental and the physical variations of psychopathic and neuropathic elements of the criminal classes, and we are to get at some principles for the co-ordination and succession of these phenomena. For the verification of the former set or phenomena, it seems best to select some opportunity where the psychopathies are more outspoken and not complicated with legal considerations, where the process

is proceeding at a faster rate. In other words, it will be best to select the material with great care.

In some particular phase of the psychopathic process corresponding to definite sets of psychomotor manifestations, the components, although difficult enough to analyze, are far simpler for investigation than the actions of the psychopathic or neuropathic criminal, complicated as they are by sociological and legal considerations We should study, therefore, some very carefully selected case furnishing the simplest and most controllable components in the process, as, for instance, from the group of neurasthenias, hysterias, amnesias, etc., or other forms of dissociations of consciousness. Working at such a case from the standpoint of a coalition of several branches of research on an inductive deductive basis, we may form some certain conclusions as to the *modus operandi* of the whole psychopathic process. These conclusions, increasing in value and truthfulness in proportion as we increase the extent of the study of the examples of psychopathic disease from which they are drawn, may be then used deductively to verify the phenomena of the defective or diseased criminal by specialized investigation. Such a scheme has at least some merit, for it proceeds according to method. It has a groundwork for construction and does not array the external facts blindly or at random.

This scheme would stimulate the student of criminology in his specialized researches, to broaden out the mental elaboration of his facts, correlating their values with other departments of science, because his guiding principles drawn from another field have to be continually in mind. He will be compelled, therefore, to use analogy and comprehensive comparisons. He must all the time compare the less pronounced phases of the functional mental phe-

nomena in the diseased or defective representatives of the criminal classes with the more outspoken stadia *along the whole pathway of abnormal mental life*. It is particularly necessary that the study of the psychopathic or neuropathic criminal be made one of the integral parts in the organic whole of a coalition of sciences—psychiatric and neurological research. This is the most favorable standpoint for criminal anthropology to conduct its researches and make advances.

In regard to the physical variations in the criminal, we might proceed in the same way as in the investigation of the mental variations, that is, it will be necessary to have some principle to start with; some preliminary guiding idea as a groundwork for the collection and arrangement of the facts of the physical variation in the defective or diseased criminal.

Very little, if any good, can be gained by simply investigating these variations *en masse*, in the way one would use a net to entrap anything that comes in its way. The statistical elaboration of human physical variations *en masse* is liable to be of no use to the investigator himself or to others armed with some working hypothesis of variation and heredity. If the study of the variations is guided by some theory of the general operations of variation, even if the theory be faulty the facts will stand a better likelihood of being available, if not at present, at least in the future, as the general study of evolution finds more and more adequate theories.

One is not to collect, elaborate and make averages of measurements of so many hundreds or thousands of criminals because it may have happened that someone else has made a fewer number of measurements or by a different method, or because it seems a golden opportunity to fill up

some minute crevice in anatomical observations. These things should be done with the distinct purpose of *solving some problem in man's biological relations*, and the statement of the problem should be deliberately formulated beforehand. To formulate the problem before beginning the observations brings out the all-important *motive* of the investigation. This motive is the guidance of the observations from a general study of heredity and variation and the states and value of the various working hypotheses of these two subjects. Without the motive the investigator lacks discipline and runs great risk of going astray and getting completely confused amid the facts collected.

How shall one find a guiding theory for the co-ordination of these physical variations among the defective or diseased criminals? By confining himself to the criminal alone, it is certainly hopeless to find any guiding principle. The facts of variations in man are indeed unique and highly valuable. Galton, the pioneer in the study of human heredity and variations, has reached many conclusions agreeing with many points worked out independently by Weismann, notably in the continuity of the germ plasm and the weak influence worked on it by the individual. But notwithstanding Galton's brilliant work anthropological studies in man alone have and can never form but an iota of the great drama of evolution, heredity and variation. Neither man nor any other living thing is intelligible if taken by itself. The phenomena of the whole organic realm are so interwoven that they must be surveyed throughout the whole series. Thus the study of variations and heredity involves the work in botany, zoology, paleontology and embryology, physiological as well as morphological. If, therefore, one would study intelligently the physical variations of the diseased or de-

fective portions of the criminal classes, he must prepare for his work by gaining some general knowledge of evolution and variation and from this select his guiding principles for the formation of his facts. A difficulty arises immediately, for none of the theories of variation and heredity are at all adequate. Prof. Osborne points out the fact that the trend of study of evolution and heredity is now seeking a more well defined inductive and experimental basis. And with this established, the unknown factors in evolution may be brought to light, more probably through the labors of physiology than of pure morphology.

The questions in evolution have been stated rather than answered, and, as Osborne says, "we are entering the threshold of the evolution problem instead of standing within the portals. The hardest tasks lie before us, not behind us, and their solution will carry us well into the twentieth century."

The differentiation of palingenic from cenogenic variations, *of the time when a variation arises in the life-history of individual*, whether in gonagenic, gamogenic, embryogenic or somatogenic periods, and the investigation of the relations of the ontogenetic to phylogenetic variations are all factors of fundamental importance and cannot be cast aside in study of the human variations in anthropological investigation of the criminal or other defective classes. In short, he who would pursue the subject of the physical variations of the defective and diseased portions of the criminal classes must be a student of evolution and heredity.

And despite the excessive complications of the study of evolution and the wide range of its inquiry and the inadequate state of our knowledge, he must seek some guiding standpoint from the present working hypotheses

in evolution at large, and proceed from it deductively in the study of pathological elements of the criminal classes. In this way even if the hypothesis has to be abandoned or modified in the future, the facts have been marshalled in an orderly way and are of service for re-elaboration, when the working theory becomes perfected. Difficult and comprehensive as is the study of variations in man in a certain small fraction of the race as in the criminal or defective classes, we may, nevertheless, hope that in the course of the deductive application of some working theory gathered from the general stock of knowledge of evolution some light will be reflected back on the general stock of our knowledge. The greater the number of standpoints sought after, the greater will be the progress, provided there is co-ordination with the diverging lines of other sciences."

While the great length of time elapsing in rendering a progressive variation continuous, is exceedingly discouraging and makes steady research in a particular instance well nigh impossible, there are opportunities for studies in man which, although limited, are nevertheless quite unique. We have in the first place the influence of experiment on the subject of ontogenetic variations and their relations to phylogenetic variations. I do not mean experiments such as can be devised and controlled by the investigator, but such as are already performed for him, by disease processes. These are in every sense of the word experiments of the most beautiful and ingenious kinds—nature's experiments. In the analysis of the several stages of formation of ontogenetic variations there certainly ought to be fine opportunities of research in the action of toxic agents, or other pathogenic stimuli (also defective cell food supplies) on the gonagenic variations

as well as on the variations arising during the several periods of embryonic development. The phenomena of immunity, predisposition and vulnerability, inherited immunity, immunity as racial features ought to be most attractive fields for the general student of evolution. Furthermore, in man the opportunity is favorable for the study of repetition phenomena or reversion phenomena as possibly in the degenerative classes in idiocy, cretinism and epilepsy. There ought also to be in man material for attention to the dependence of ontogenetic *repetition* upon repetition in the environment and life habit, in contrast to the connection of ontogenetic *variation* with variation in environment and life habit. Particularly valuable would be the study of generations of delinquents in families, as in the remarkable investigations of the Jukes family.

The prison often contains inmates fit to be patients in the psychopathic hospital. Quite likely the psychopathic processes and certain portions of the criminal classes may reveal the initial stages of the process of neuron energy liberation, only here the process is spread out through a greater length of time. The ebb of neuron energy may have occurred through generations, and the neurasthenic phenomena concomitant with unloosening of the highest constellations of neurons having to do with inhibition, and the duties of *morale* and the guardianship of the finest and noblest of human emotions may occur most insidiously. The expenditure of neuron energy sinking in the course of many generations by almost infinitesimal and unnoticeable descents over the restitution-ascents of energy,* the higher neuron constellations in some particular man in a series of generations may utterly fail to develop the mechanism for elaboration of energy. Hence their parallel powers

* See paper on "Neuron Energy."

will be utterly lacking. Such a man may have no sense of morality and discipline and his subconscious self may tend to come out in all its nakedness.

I am not intimating here a transmission of acquired characteristics, that is that the receding tide of neuron energy in any individual influences the germ plasm to any extent. The external causes that liberate neuron energy in the individual affect the germ plasm simultaneously. These causes operating first in the highest and most unstable neuron may, to some slight extent, operate on the germ plasm in a secondary way from the damage to the neuron constellations. For these being progressively impaired both in extent and degree by the continuance of the external causes the general body forces (circulation, general metabolism in cellular food supply) may fall below par, and in this way exert a modifying influence on the germ plasm. But I prefer to think that the changes in the germ plasm passing on the continuance or preparation for the neurasthenia of the next generation are directly due to the same external causes such as toxic agents, deficient food supply to neuron that will bring about an undue liberation of neuron energy. The changes in the germ plasm are less dependent on the pathological expenditure of higher neuron energy than on the action of the same causes that also affect the neuron.

It seems to me that there are points of similarity between ordinary neurasthenia and the psychopathic conditions of certain criminal classes. And I think we may take it for granted that observation shows that some of the criminals certainly show psychopathic and even neuropathic phenomena. If we conceive that the ordinary type of the neurasthenic phase of the psychopathic process be stretched out through a greater space of time, so that it

is exceedingly chronic and insidious, we have a mental picture of what may be taking place in the psychopathic criminal and what leads him to do his acts. This is not a mere speculation, for it is based on the general theory of neuron energy alluded to previously, derived from a certain range of facts forming a supporting groundwork. It is not at all difficult to conceive of the neurasthenic manifestations and their concomitant phases of the underlying pathological process as being more spread out in space and time (through members of generations) than we ordinarily witness in the symptoms in the concentrated phenomena in the ordinary form, occurring as an attack in a part of the life-history of the individual.

I am far, however, from making any sweeping application of the psychopathic basis of criminal acts, for who is to pronounce judgment upon right and wrong, or to give a standard of goodness in mankind? We can only look at the extremes, more or less, in delinquent actions. It seems best to seek out the more outspoken psychopathic cases in the prisons, and investigate them as comprehensively as possible, under the guidance of the neuron energy theory. The factor of environment is, of course, included in the study of the criminal in speaking of the guidance of the investigation from the standpoint of evolution. Anthropological investigation of this kind of the criminal, of the delinquent and defective classes may possibly prove valuable and fruitful. "Pathological anthropology," (by this I understand the study of human variations from the basis of pathology) is especially dependent for its success on a correlation of sciences after some such plan as we have endeavored to outline for psychiatric research. It is hard to see how anthropo-

logical investigations of this special kind can make any headway.

In centres of psychiatric research, criminal anthropology comes prominently to the surface in the direct and specialized investigation of the insane. For many systems of caring for the insane have to take into consideration the criminal insane and the insane criminal. In our own system, for instance, there is one special hospital set apart for the criminal insane. Here is a most valuable opportunity for getting at the borderland between the psychopathic criminal and the insane classes. Here is a class where the descending process of neuron energy liberation is outspoken and comes obtrusively to the surface. From this pivotal point the investigation should work in two directions: upward along the psychopathic channel toward the initial stages where the process approaches normal mental life, and downward in the abnormal mental life into deeper and deeper levels of insanity, both neuropathic and organic.

It seems to me that the hospital for the criminal insane offers the most absorbing and fruitful field of work for the anthropological psychiatrist. The differentiation between the criminal insane and the insane criminal seems to hinge upon a very insecure scientific basis. It is simply a question as to when the insanity was detected; if the individual committed a crime and there is insanity detected he is an insane criminal; if his insanity is first detected and then the crime is committed, he is a criminal insane. Both are of the same order, and their difference simply depends on the thoroughness of the examination. This distinction is therefore an arbitrary one. Further researches are greatly needed in the criminals exhibiting psychopathic phenomena. The diseased or defective criminal should

be studied by the methods of psychology and psychopathology.

In regard to the inter-relation of the abnormal mental phenomena or mental variations with the physical variations, caution must be used lest one stumbles into pitfalls of error, and allows the fallacies of the simple method of enumeration to insinuate themselves into the elaboration of the facts. If one starts out with the idea that the mental departures in the criminal are in some way linked with the physical variations, both operative from a common cause or set of causes, it becomes easy to support the idea by collecting the instances which support the theory, and overlooking those which contradict it.

In statistical elaborations especially, this tendency to a greater or less degree, is often prone to occur. Among a large body of criminals the relation of physical variations to initial psychopathic phases might gain undue weight, unless we ascertain how far possibly the same set of variations may also occur in non-criminal classes, not associated with any psychopathic taint.

It might seem theorizing in advance of the facts that errors in the molecular structure of the germ plasm would first tell on the most supremely organized parts of the body (the highest congeries of the neuron constellations in the frontal lobes) without showing defects elsewhere in the body. It would seem that defects in the highest parts of the nervous system might occur without corresponding defects in the body. Conversely morphological defects in the body of any considerable degree would connote defective brain development. Facts show, however, that this may or may not be the case. Féré* has shown experimentally, that certain influences (noxious vapors,

* Bulletin de la Société de Biologie, 1896, p. 790.

mechanical vibrations) harmful to development if applied in a certain degree, may be favorable when applied in a lesser degree. Thus it seems that agents capable of exerting an influence resulting in an arrest of growth in one part may in the total development produce a superior individual. What is a drawback in one part may be a gain to another. Thus, some individuals with partial defects, have a remarkable general constitution. Hence, one often sees great minds dwelling in frail or ill-formed bodies. On the other hand, the agencies which we may imagine of a kind similar to those studied by Féré experimentally in the egg, may be of such a degree of intensity (auto-intoxications of the pregnant mother, other toxic and pathogenic agents and disturbances in the cellular food supply brought to bear from the mother to the fœtus) as to cause retardation of development without compensation in the nervous system or elsewhere. In this way weak individuals would be born without any saving graces. According to these experiments the matter hinges on the intensity of external agents.

Féré notes in harmony with his line of thought that the most civilized nations are distinguished by the number of extremes and exceptional beings: men of exceptional mental power, geniuses, and others intellectually and morally pervert. These latter are so because of deficient energy of the highest spheres of the brain unveiling in periods of time spread through a single individual or throughout generations the subconscious self which Sidis characterizes as "cowardly, brutal, credulous, suggestible, and devoid of all morality and conscience." These variations discussed by Féré, however, are to be carefully distinguished from the reversions or repetitions of variations. The inter-

relations of the physical and mental variations are enormously complex, but with what is known of the laws of mental life, heredity, and variations, or with such approaches as have been made toward these laws by psychology and the study of evolution to guide the research, we shall go less far astray by restricting the investigation to the criminal and endeavoring to find guiding theories in the restricted sphere of criminal anthropology alone.

It is somewhat customary in examining from time to time the status of a science and regarding its future progress, to look back into its past history and to go out of one's way by quoting selected passages from older observers, to show that they had premonitions of the knowledge of the present day. These retrospects are exceedingly interesting, but in most cases they are hardly worth the while, for in the past fifty years in many sciences the knowledge is quite divergent, and indeed is often totally different from that of the preceding periods. The reason is, the methods of investigation are now totally different; they are more exact and of more extensive scope. The past of criminal anthropology is interesting, however, for it shows that the subject is worthy of a division of labor in the community of sciences, and should be given the attention of a distinct science of its own. There has been a steady growth leading up to the formation of the science of criminal anthropology and its pedigree is quite old.

Plato and Aristotle made studies of physiognomy and attempted to work out the physical and psychological correspondence of the passions of men and their facial expressions. From these early studies to comparatively recent times there have been numerous attempts to estab-

lish a relation between certain physical (anatomical) conditions and abnormal psychical states. As a result, however, of the isolation of these investigators and their dependence on speculations in lieu of adequate methods of studying facts their studies present much repetition and consequently useless work. Notwithstanding this it is possible to trace in these and later works a gradual growth and a steady advancement which forms the basis of our present view of the unstable classes. Upon these works criminal anthropology was founded.

The study of the criminal has not leaped into a sudden or distrustful existence, but has behind it the momentum of centuries of thought along the idea of the linking of man's physical and mental variations. The study of physiognomy was revived by the Jesuit Niquetius, by Cortes, Candamus, De la Chambre, Della Porta, etc., who were the precursors of Gall, Spurzheim and Levator on the one hand, and on the other of the modern scientific study of the emotions with their expressions, in face and gesture, conducted by Camper, Bell, Engle, Schaffhausen, Schack, Heiment, and above all by Darwin. Gall's theories were applied in the examinations of criminals by Lauvergne (1841) and Attomyr (1842), but they carried the figments of phrenology to the extreme. DeRolandes (Italy, 1835) published observations on a deceased criminal; Sampson (America, 1846) tried to trace the connection of criminal phenomena and cerebral organization; Camper (Germany, 1854) published a study on the physiognomy of murderers, and Lallement (1858–1862) published a long work on criminals from a psychological point of view. The science of criminal anthropology, strictly speaking, only began with Forbes Winslow (1854), Mayherr (1860), Thompson (1870), Wilson (1870), Nicolson, Maudsley (1873) and the

notable observations of Despine (1868) and finally of Lombroso.

Since 1876 a number of writers have published valuable additional studies of the criminal, and have established the fact that indications of psychopathic and neuropathic processes frequently appear in individual members of this class. Experience also demonstrates that quite a share of crimes are committed by persons who are insane in the ordinary acceptance of the word, or at least who may be said to have the prodromata of insanity. In addition to the prison we have in mind the extension of anthropological work in the reformatories among the refractory and delinquent juveniles, the epileptics, the deaf and dumb, and the blind, or secure co-operation in work from those having charge of these classes. Among the idiots the work ought also to be very promising, and throw light upon the *modus operandi* of this effect, and especially upon their classification, unless this has been worked out satisfactorily by such investigators as Sollier, Petersen and Ireland. One quite certain indication of the increasing momentum of the study of criminology and allied subjects is the appearance of special journals on the subject. Germany and Italy each have a journal for the dissemination of the accumulating knowledge on this subject.

The great difficulty encountered in this investigation is the selection of a normal standard whereby to measure the abnormal departure. In this country where the population is so hetergeneous, we are immediately confronted by the difficulty of finding a standard race type to measure by, and in fact we can find no absolute standard. Only a standard varying between certain small limits can be used. We also hope by means of this department of

anthropology to study the phenomena of deterioration in the criminal and in the epileptic.

Immediate results can hardly be expected from this department. The amount of work falling within the scope of anthropological investigations of the early phases of insanity is stupendous. It can only be done little by little, and must grow and develop in the course of years. Any work along these lines such as previously indicated, to be of any value whatsoever, must be most carefully planned. It cannot be forced along with undue haste. One must, therefore, ask patience in expectation of results from this branch of investigation, the more so, since there is no well defined and no established precedent to follow. The work is of a pioneer character, and this as a rule meets with failures, and often has to begin over again, profiting by its mistakes, and has frequently to readjust its plan and methods of work. From time to time results may be published as to the progress of this department, but they cannot be had all at once.

A very interesting piece of work now in progress in the department of anthropology is a study of the correlation of the mental and physical growth of some young boys in a disciplinarian school. This has been undertaken in conjunction with Doctor Downing, of Brooklyn, N. Y. Fortunately we have an opportunity of studying these boys for several years, in order that we may fully record the relationship of psychical and physical growth, and also identify those among them who tend to deflect into the pathway of degeneracy. In short, the main object of the department of anthropology is to identify and study by means of scientific methods the degenerate, the candidates for the prison, the reformatory and asylums. It must be seen how important is some attempt at gaining

a coherent knowledge of the insane before they make their way into the hospitals. When this is known, it is bound to be of practical benefit and yield economical returns by instituting some form of control of insanity before it reaches its more hopeless stages.

In brief, one prominent purpose of anthropology at the Institute is to ascertain the proportion of cases of insanity occurring in normal individuals, in individuals who have no hereditary predisposition toward insanity—and to compare this proportion with the other cases of insanity complicated with or resulting from hereditary predisposition. For in the former class of cases insanity is more or less of an accident, and in the great majority of cases recovery is to be expected; whereas in the latter class with predisposition recovery is much less liable to occur. The determination of this question is most important.

The instruments required for this department are comparatively simple and inexpensive. It has apparatus for testing the acuteness of the senses and sundry instruments for physical measurements of the human body; two instruments to measure the diameter and contour of the skull, one in duplicate for the use of the State hospitals; measures for determining the cubic contents of the skull; a stereograph for tracing contours and profiles of the skull, and an anthropometer used for taking general measurements of the body.

We hope in the course of time to make a collection of skeletons of the insane, in order to study the stigmata of degeneracy in the osseous system. These skeletons can be exhumed without much expense, after the cadaver has remained in suitable soil for two or three years.

The anthropological institute at Paris is very proud of

the collection of the complete skeletons of thirteen epileptics, because their histories and behavior during life are accurately known. Seeing that the histories of our patients at the hospitals are scrupulously kept, we ought to be able in the course of time to have one of the best collections in the world for studying the osseous systems of epileptics, criminals and lunatics. The value of this collection does not lie in the fact that it is a mere conglomeration of bones, but that it should be possible to study each skeleton in connection with the life-history of its possessor.

The department is in charge of Alois Hrdlicka, M. D.

Chapter XIII.

THE UNCLASSIFIED RESIDUUM.

In concluding these remarks on the correlation of several branches of scientific research in the investigation of the life-history of insanity,* a paragraph from one of Professor James' essays† is most appropriate.

"The great field for new discoveries," said a scientific friend to me the other day, "is always the unclassified residuum. Round about the accredited and orderly facts of every science there ever floats a sort of dust cloud of exceptional observations, of occurrences minute and irreg-

* It should not be considered that a centre of psychiatric study, such as the Pathological Institute of the New York State Hospitals, has overreached itself in bringing unnecessary or irrelevant departments of science to bear upon the problems of psychopathology and psychiatry, or that in taking a stand against the restricted study of insanity it has gone to the opposite extreme in too greatly diversifying this research. The fact that there is no assistant in psychology and psychopathology, that there is but one associate for the whole comprehensive department of pathological anatomy, and that there is no representative for the department of normal histology of the nervous system nor for experimental pathology and hæmatology, shows that this projected plan of the correlation of branches of scientific research in insanity at this Institute is still not completely developed.

† "The Will to Believe and other Essays in Popular Philosophy," p. 299.

ular and seldom met with, which it always proves more easy to ignore than to attend to. The ideal of every science is that of a closed and completed system of truth. The charm of most sciences to their more passive disciples consists in their appearing, in fact, to wear just this ideal form. Each one of our various *ologies* seems to offer a definite head of classification for every possible phenomenon which it professes to cover; and so far from free is most men's fancy, that, when a consistent and organized scheme of this sort has once been comprehended and assimilated, a different scheme is unimaginable. No alternative, whether to whole or parts, can any longer be conceived as possible. Phenomena unclassifiable within the system are therefore paradoxical absurdities, and must be held untrue. When, moreover, as so often happens, the reports of them are vague and indirect; whether they come as mere marvels and oddities rather than things of serious moment—one neglects or denies them with the best of scientific consciences. Only the born geniuses let themselves be worried and fascinated by these outstanding exceptions and get no peace until they are brought within the fold. Your Galileos, Galvanis, Fresnels, Purkinjes, and Darwins are always getting confounded and troubled by insignificant things. Any one will renovate his science who will steadily look after the irregular phenomena. And when science is renewed, its new formulas often have more of the voice of the exceptions in them than that of what were supposed to be the rules."

Surely from the scientific standpoint the disordered states of consciousness in insanity form a very large "unclassified residuum." In correlating the branches of sciences we have avoided the danger indicated by Professor James, namely, the restriction of a branch of science to some

fixed and narrow limits of observation. If a branch of science be thus restricted it soon becomes walled up within itself. It travels in a rut, repeats its old observations over and over again, trying to make them appear new by merely setting them forth in new words, or what is still more deceptive, marshalling and exhibiting them in diversely colored plates of differently stained sections; it finally becomes worn out and mummified. On the other hand, if a branch of science seems to be nearing the limits of its capacity to formulate new generalizations, when it seems to have completed its possible activities in presenting the ideal "closed system" of truths to which there seems nothing to add, such a science, when extended to the outlying domain intervening between a sister science, may have to begin its investigations all over again in a new and broader light. *Modern specialization among the branches of science is creating gaps and clefts which contain more important fields for investigation than the individual departments of science themselves.* He who can bridge over the rifts between the border lines of several of these sciences will discover the richest domains of investigation and gather in a good harvest of scientific truths. *It is the value of the domains between the various medical and biological "ologies," when guided by psychology and psychopathology that we have endeavored to bring into prominence in the study of insanity.*

Chapter XIV.

THE FUTURE OF PSYCHIATRY.

We have pointed out some of the natural shortcomings of psychiatry, inevitable in the evolution of its progress; we must now behold the greatness of its future. It would be a carping and disrespectful form of scientific *lèse*

majesté to point out the shortcomings of psychiatry as a stigma on the name of the science, for it is truly destined to be the most majestic of all the biological and medical sciences.

The shortcomings of psychiatry only serve to show the greatness, comprehensiveness and difficulties of the science. The other sciences in medicine and biology are elementary beside psychiatry. They are but stepping-stones to psychiatry and psychology. For the two are synonymous in studying the abnormal phenomena of consciousness. Psychiatry should never be so narrowly viewed as being tied down only to insanity, it also deals with abnormal phenomena of consciousness in general, the domain of psychopathology. The study of abnormal manifestations of consciousness presupposes some knowledge of normal psychology while at the same time it is the only key to an understanding of normal mental phenomena.

It is not strange that psychiatry, the most difficult and comprehensive of all medical and biological sciences, has been one of the last to begin its scientific progress. Psychiatry has not lagged behind of its own accord; it has been held back and had no choice but to wait until its stepping-stones might be built. It has had to wait for the growth of psychology in general and psychopathology in particular; it has had to wait for cellular biology, pathological anatomy, neural anatomy, and their affiliated branches of research to attain sufficient development to cope with the difficult problems of psychiatry. Psychiatry for the short history of its existence has done its utmost with the imperfect methods at its disposal, and is now looking for new methods to fertilize its soil, highly fruitful, but difficult to till. When it is perceived how far the subsidiary sciences have had to develop before attaining

the capacity to be of service to psychiatry, we can gain some idea of the eminence of psychiatry among the medico-biological sciences.

Psychology, psychopathology and psychiatry are destined to form the loftiest pinnacle of the temple of science. The scientific story of the rocks holds one spell-bound; the history of the egg or the mechanism of a tiny organism have their fascination; mathematics and the laws which command the courses of the stars are awe-inspiring, but none of these sciences or their allies have the grandeur or are so deeply and essentially human as the three sciences—psychology, psychopathology and psychiatry—for they unveil the greatest marvel of the universe—the human mind. Well may we say with the great Scotch philosopher: "In the world there is nothing greater than man, and in man there is nothing greater than mind." A knowledge of mind, both in its normal and abnormal manifestations, is the science of sciences.

The common run of neurologists and pathologists, in their mistaken nature of the true function of science, lose more and more sight of what lies beyond their microscopic field of vision. What is still sadder, they are absurdly proud of their narrowness, making a virtue of their shortcomings; their ignorance is as great as their conceit is infinite. They highly value the process of groping aimlessly in the dark for new details. All explanation, all rational interpretation, is shunned as a pest, and under the stigma of "theory" is kept in abhorrence; all comprehension of phenomena, all generalization, is branded by the name of "metaphysics" and is sneered at, and ridiculed, and held in contempt. The more meaningless, the more inexplicable a detail is, the more is it treasured and valued as a "good fact" purified of all extraneous dross, such as reason

and understanding, which are branded as a vice, as "theory and metaphysics." And yet these very neurologists, histologists and pathologists who suffer from intellectual photophobia or phrenophobia are the worst type of dogmatists, the least intelligent class of unconscious metaphysicians, inasmuch as they revere only the chaotic, the irrational and the incomprehensible. It is only the best thinking men among them who begin to look for light and for a broad horizon. The psychiatrist, on the contrary, by the very nature of his studies, is forced more and more to broaden out the basis of his science. Nothing short *of a co-operation of all the medico-biological and psychological sciences* is what psychiatry requires. The enlightened psychiatrist looks for an *organization* of the dispersed and dismembered parts of medical science. Medicine has usurped the psychological guidance of psychiatry altogether too long.

Fortunately this enlightened spirit found a foothold in the Commission and the representatives of the New York State Hospitals, and for the first time in the history of science was an Institute established on a broad scientific basis, an Institute whose aim is to till the field of psychiatry by means of instruments and methods obtained through an organized federation of the most important and most vital branches of biological and psychological sciences. Such a federation is not only indispensable to the growth of psychiatry, but is also most essential to the development of biology, psychology and exact medical knowledge in general. Men of science ought to be grateful to the psychiatrist for the mere fact that he is the first to call for a *general unified* activity of many branches of science. For *unification* means *generalization*, the discovery of *laws*, the true aim of science.

PART III.

Chapter XV.

FACTS AND THEORIES IN MEDICAL SCIENCE.

When a scientist ventures into foreign fields, he can return to his own particular territory with new and broader ideas and recast his whole trend of observation; he becomes possessed of the power of larger guiding principles; he has the great advantage of guiding his work with discrimination and of seeing what is essential, passing by what is accessory; he sees better through the relation and interdependence of things instead of trying to hit upon them by shuffling the facts about; he has a discontent with the scope of his former work and seeks to look further beyond the proximate into the remote. Such a spirit of discontent is the watchword of progress in science.

Meanwhile the venturesome traveler must expect distrust from those who are working in these other fields; for both they and he know that only the crust and the surface are being inspected by the outsider who can have no grasp of the depths and the details. On the other hand, he must also expect to be openly or secretly discredited by his colleagues who remain at home quietly working out their results, and must also expect to be looked upon as having fallen behind in the ranks, because he left the work desk and the machinery idle for the sake of reflection. He is liable also to fall under the stigma of having been affected by unsound ideas; and although this should entail caution, it is not to be held in excessive apprehension. Altogether the task of broad generalization and correlation is not inviting, and, besides, the great labor, the distrust and opposition met with, make one

averse to undertake such a work. If the journey be at all extensive, it will indeed be strange, if one does not return with a burdensome sense of oppression at the vastness of what lies before him in other strange pathways. The pioneer in science may feel like Humboldt bewildered at the fathomless depths of nature, not knowing where to pick up the guiding threads for explanation.

In this cursory glimpse of a few departments one cannot help feeling great dissatisfaction with the way the subject of the importance and value of correlation in psychiatry has been presented. Many points of importance have been barely touched upon and others have been entirely omitted. Yet no such vast plan was ever entertained of attempting a comprehensive sweep of so many sciences. The attitude has been to look at the borderlands of the branches of research, to glance at their confines and at their points of coalescence, and from this to gather ideas, guiding principles and methods whereby psychiatry might open a new pathway. With some key, some broad idea derived from a study of consciousness and fortified by some psycho-physiological principle, we work deductively and use the phenomena in psychiatry for verification. In this deductive process these several sciences would also be of use in the verification in their several bearings on abnormal mental life and also reflect light on the theory from an inductive standpoint.

A thing that has augmented the dissatisfaction with this writing almost to the point of discouragement is that certain matters have been accorded a prominence and emphasis which in a little while will surely seem obvious. It may be, however, that what seems exceedingly elementary in some places, as befits a discussion of this character, is somewhat balanced by being interwoven

in other places with ideas that are not wholly superficial. I think also that in a little while they who secretly and openly discredit such an ideal, because it has not fallen into the conventional and hopeless groove, will be the very ones to take the whole plan of the correlation of sciences in psychiatry for granted, as an indispensable and obvious means of progress, as is usually the case with all departures from the beaten track. Yet at this particular time one finds it necessary, elementary though as it will appear a few years later, to defend the use of the several branches of research in their correlation and organization for the benefit of psychiatry.

One may get suggestions of deep application and pivotal points to work out brilliant theories in disease process by reflecting on the analogy of the human commonwealth of cells with the social organism. Take out the factor of correlation and interdependence of the parts, and progress stops—the organism, social, living or scientific, falls to pieces. Restrict psychiatry to the microscope, and it is impossible to gain the momentum and power of the correlated sciences—aside from the fact that from the very nature of microscopic research, it is not even on the right road to solve the problems of abnormal mental life.

At one moment psychiatry is taken to task, because it does not progress, at the next moment, because it does attempt progress. The attitude is absurd, yet unfortunately on the ground of expediency, it is also to be feared. It is to be feared, because it measures the work of an institution of this kind by the false standard of simple mechanical fact-gathering mainly through pathological anatomy. This is unfortunate, but it cannot stay the progress of psychiatry. Progress in psychiatry is bound to come, it is inevitable.

There is a great difference between "work in science" and "scientific work." In "work in science" mechanical work is at a maximum, and reasoning at a minimum; in "scientific work" the reverse is the case. Shall work in pathological anatomy and bacteriology remain the main avenue of scientific psychiatric research? Shall we have men satisfied with the act of pouring forth into the already swollen streams of literature desultory microscopical details, the real task, the true aim of science, being left undone? Is there not already enough of such work, in medicine, or is the work to create what might seem an admirable spirit of emulation by detailed description of minuteness outdoing the devils of whom it is said that some twenty thousand can dance on the point of a needle without causing the least friction? We do not get explanation by miniaturing the problem. If the microscope could get down to still smaller particles the same old question is still on hand, as to why the particles dance and what makes them dance.

What becomes of many of such descriptions after they are discharged into medical or psychiatric literature? After the first ephemeral notice is passed, they are shelved with the rest of the lumber to be dusted off occasionally, when someone else on a like errand compares them with his own results showing wherein he agrees and also wherein he disagrees. The title of the work also adorns its appropriate line in the bibliographical annex of other papers.

When the collection of facts is to be made use of, observe what is done by the man of ideas. He quietly appropriates the work and puts a value on it. Armed with a play of the imagination, he makes a mental elaboration of the facts; interweaves them with theory.

Meanwhile from the men of facts a storm of disapproval comes. They are grieved, because they think they have done the real hard work and a marauding theorist has plundered them of it. What aggravates the matter is that the man of ideas seems gifted with a strange and vexatious ingenuity of eliciting what he can make use of, what fits in and dovetails with his ideas.

Often, however, perhaps as a rule, the desultory "new" facts collected by the "workers" remain in their chaotic and worthless state,—they cannot be utilized by the man who works from the standpoint of ideas and theories. This is because when facts are described and catalogued by the workers, that which is frivolous, inconsequential, and accessory, is given just as much weight as that which is essential and of pivotal value to test a theory. The worker cannot separate the indifferent from the essential. How can he appreciate the essential without knowing what he is striving after or not having any idea of what he wants to prove and solve? In pathological anatomy, for example, is there not amid the plenty of facts a dearth of ideas? Do we gain, for instance, anything by saying that in hyperplasia the tissue grows, because the inhibition to growth is removed? This subterfuge does not explain anything. And yet the phenomenon has a deep significance when its explanation is realized in the light of a broad range of thought.

The students of pathological anatomy make a mistake in studying man by himself and as a species discontinuous from other forms of life. The study of an animal is not intelligible when the animal is taken by itself, away from its environment, out of its place in the whole range of animal life. If medical men have fallen into the habit of believing that the microscope is the guide to

medical science and that pathological anatomy is the great and main line of investigation, must psychiatry also follow suit, or rather, remain in the same rut? If in medicine the idea is prevalent that descriptions of the facts of abnormal structure accomplish the main aim of scientific research, must psychiatric study be discouraged, because it would abandon this delusion? In science the influence of the beaten track must not arbitrarily repress that which departs from it.

It is very sad to find that some medical men, men who ought to know better, are under the delusion, prevalent only among the least educated classes of the profession, that the main point of science in general consists in recording facts in pathological anatomy and bacteriology. The same thing is expected of psychiatry and all original research work that does not follow the beaten track of medical science is abused and decried. But how will the advance of psychiatry be attained by recording facts in pathological anatomy? To attempt to make the study of pathological anatomy the guiding motive of research in the phenomena of abnormal mental life is a snare and delusion, sheer folly.

The demand to throw out on the would-be scientific market a mass of incoherent facts, as if it were accomplishing the real work of science, is unreasonable. Dumping facts into so-called scientific medical literature would have been an easy and simple matter. Indeed, a great number of facts have been gathered at the Institute by a great variety of methods. The brain has been thrust into the crucible and its ashes determined, it has been rended with acids and alkalies, it has been preserved in many fluids and stained with many dyes, giving rise to many plates with diversity of color; guinea pigs,

monkeys and rabbits have had their share of toxines and bacteria; in fact it appears that the particular demon presiding over a certain form of meningitis has been caught, registered, put in the culture tube, and given a proper place among his associates in the bacteriological collection. Yet how does the mere statement of all these facts in any way explain the phenomena of insanity? Which is it best to do? Pour out these facts into the literature just as they are found, or attempt to co-ordinate, arrange them in harmony with theory, and endeavor to see their relation to the problems of abnormal mental life? We have endeavored to maintain a higher ideal than to record facts blindly.

The aim of this Institute is not to collect blindly and irrationally masses of incoherent facts and of confused new details, the cherished ideal of the school or rather of the crowd of the so-called scientific "workers." The Institute is a scientific centre and as such it aims to cultivate science in a rational way making use of inductive and deductive methods, guided by theory, hypothesis and speculation; it works at facts in order to solve a problem, in order to make use of the facts and not merely to collect them without separating the chaff from the kernel. The facts collected, whether of our finding or discovered by others, are as far as possible governed by guiding principles, broad theories, theories consistent with the body of knowledge gained in other directions. If the study of facts is not guided in this way, it is hard to see, no matter how fine the details and how close the observation, how such blind recording of facts can possibly avoid confusion. On the other hand, one must fully understand the danger of ill-founded speculation, of speculation wrought out of a limited and specialized range of observation, of speculation announced without sufficient verification.

Some medical men have queer notions of the meaning of "work" in science. In all other walks of life work must have a definite purpose—only in science work should be done blindly, without any aim, work for the sake of the work itself. If in life we require understanding of the work and knowledge of its purpose, the purpose guiding the work, why should ignorance of purpose be considered a virtue in science? Are blindness and ignorance special attributes of medical science? Most certainly not.

In this age of feverish activity hundreds and hundreds of men are working in an almost delirious haste in laboratories scattered all over the civilized globe to obtain priority of recognition in the discovery of new facts. Great masses of desultory, fragmentary, inco-ordinated descriptions of facts are recorded in scores of specialized journals. Even in the same laboratory men are working side by side and still independently isolating their fields of inquiry. Their chief aim seems to be to find something that no one else has worked upon, in order that it may be *new*, however insignificant it may be otherwise. Most of all, instead of suspecting where to find the new facts by premeditation, they expect to hit on them by the doctrine of chance, by straining everything that comes along in their nets in the hope of finding something new that may be described. The chief ambition of these workers in science is to dump into the literature four or five times a year a mass of inco-ordinated facts. Surely it were better, if the energy expended in this haste and hurry of announcing and recording details were employed in co-ordinating the facts before publication.

In the midst of all this, is it not well to pause and reflect that in the feverish fact-collecting activity we run the risk of losing sight of the true aim of science? Students

are too prone to take it for granted that the aim of science is fulfilled by the mechanical labor at the work desk and dexterity with technical methods; they are often absolutely innocent of the true aim of science, namely, generalization.

Science seems to be a race for new details, and when these are found the inquiry is at an end. Bacteriology has joined in the game with pathological anatomy, and the prize is given to the man who can catch a new devil, presiding in tutelary fashion over some disease entity, and bottle him up in the culture tube. To identify the proximate causes of disease is of enormous value from the standpoint of utility, but one must not deceive himself in thinking that this explains the process, the *modus operandi* of abnormal function.

Pathological anatomy has more need of new theories than of new facts. I hope this intimation that pathological anatomy is making the mistake of thinking that fact-gathering fulfills the true aim of science does not seem hasty, or reckless. Among the several branches of science reviewed, I feel less utterly confined to the surface of the inquiry of this department, and, thanks to my master, I have also had the opportunity of having some insight into its philosophy. Hence reflection over its deficiencies does not warp the vision of its strength, its scientific dignity, and its achievements. But these achievements must not blind us to the fact that science does not make progress by studying proximate causes only; nor are we to fall into the habit of believing that unreflective observation, no matter how close, or voluminous, fulfills the true purpose of science. There must also be the *reflective formulation* of the observations. To find truth, to discover law, thought and reflection must be used.

I do not mean to say that pathological anatomy has no

theories. It uses deduction in its own special line of inquiry; and this is just the trouble. The theories seem well grounded, if surveyed by the narrow extent of territory from which they are drawn, but when tested by a wider range of thought, they are inadequate and even absurd. The theories are derived from causes which lie too adjacent to the effects. Hence the pathological anatomist is continually turning out new facts which he cannot make use of.

Some of the pathological anatomists have not the first, most elementary notion of the purpose of science, namely—*generalization of facts and deduction of laws.* Many so-called scientists are only concerned with getting the facts catalogued. Pathological anatomy is in much the same condition that biology was before Darwin's time; like pre-Darwinian biology it consists of an appalling mass of facts, piled up by hundreds of men working in many independent, highly specialized fields, all striving to get hold of "something new." Instead of being properly co-ordinated before being published, all this is thrown into the literature just as it is fresh from the work desk. What a great opportunity it is for some one with grasp of mind to enter the field of pathological anatomy with a great general co-ordinating principle to unite these scattered facts and give them their appropriate theorectical valuation. Such a man can spare himself the trouble of delving out new facts. He may have to go, occasionally, to the laboratory desk, but then it will be with the distinct purpose of seeking some pivotal fact; some crucial experiment to test his theory.

The pathological anatomist has not only fallen into the mistake of thinking that his science consists of mere purposeless fact-gathering, but he is also leading general medicine astray. Pathological anatomy and especially

bacteriology from their lack of broad theories, instead of correcting the mistake, have only helped to confirm general medical belief in the erroneous conception of the nature of disease. Diseases are looked upon as entities, individualities, specific things, each with its specific cause or set of causes. Contentment with this idea of the proximate cause of disease simply wards off inquiry for wider generalization of thought. The narrow views of pathological anatomy and bacteriology dominate too much the whole trend of scientific medical thought.

Pathological anatomy, setting too much store on the simple task of observing and gathering facts and too little on ascertaining their significance, and general medicine, looking too much to this branch as its guide, it would be strange, if medicine did not come to be more confirmed than ever to look upon this "collection" work as the true standard of scientific research. So indeed it has happened. In medicine it is taken for granted that all of its branches should conform to the same standard and conduct its researches after the example set by pathological anatomy. For pathological anatomy and bacteriology have done grand service for the art of medicine. It would also be strange, if under this medical conception of science, theory and speculation were not greatly distrusted. This is also the case. Attempts to theorize are not infrequently held up to ridicule and scorn and considered prejudicial to the advance of science. It is certainly unfortunate that in medicine art is guiding science.

We go on discouraging theory and speculation, and yet this is the soul of science and the mainspring of its progress. We go on warning each other against philosophy in science, yet without philosophy there is no science.

Johannes Müller says of physiology that without philosophy it is no science at all. We must, however, remember that men naturally fall into two classes. By far the greater number have minds that can only concern themselves with the adjacent and the proximate. The synthetic mind that looks above and beyond the immediate and the surface of things is unfortunately a rarity, a form of genius. We should encourage this form of genius and provide suitable environment that it may thrive. We go on discrediting those who come from foreign fields of research to work in our own particular territory, yet I think we ought to welcome these outsiders who come to look over our facts and take a comprehensive glance, perhaps, not a profound view of our work, as they are often better equipped to theorize over our facts than we who are deeply immersed in some fragmentary, dismembered part of our science.

Chapter XVI.

THE PATHO-ANATOMIST AND THE CLINICIAN.

The great science in medicine is general physiology and pathological physiology in particular. It is in biology, general physiology and psychopathology that the philosophy of medicine is to be sought. *Function presupposes structure.* If we would understand disease, we must naturally study the living phenomena. This the clinician does, and the scientific clinician is in fact a physiologist and psychopathologist, for he studies function. And he is in a far better position to perceive the great guiding principle—in the study of abnormal manifestations—the energy basis of function, than the observer with the microscope. The pathological physiologist, or, if you please, the clinician, perceives the actual manifestations and activities of the disease process, whereas the man with the microscope only

sees the tracks of it, the footprints as it were. The one studies dynamics, the other the statics of disease. The study of the footprints of energy is valuable; it is a study of the effects of the process, but not of the process itself. If one would understand the footprints, he must also study the thing that made them.

The pathological anatomist often feels sorry for the clinician because the latter does not set much store by the "granules," yet it is interesting to watch the clinician use the microscope. He gains an idea from the observation of the living phenomena and uses the microscope with a distinct purpose, and as a means of verifying his idea and casting light on it. He seems quite indifferent to many ultra details of structure which the anatomist guards with great jealousy and the want of which is evidence of a lamentable lack of knowledge and held up as a warning against intrusion into a foreign precinct. But the clinician is like the physicist seeking to explain the activities of a mechanism, why and how it works, and what animates it. The color the mechanism is painted with, the oil spots, the dust marks and the like facts which the type of the mechanical, unreflective anatomist would lay equal stress with the other parts, the physicist cares very little about; what he wants to know is the general construction of the machine, and in explaining its working, he talks in the language of physics and in terms of energy.

When the scientific clinician finishes with the microscopic work, one is liable to find that it has contributed some explanation of the disease process, a thing so often left undone by the anatomist, because he cannot guide his work and fully understand the facts without a general knowledge of function and its relations to energy. Meanwhile, the anatomist observing the crudeness of the

clinician's technical methods with the microscope (which, of course, is not to be commended), is inclined to think that the clinician's conclusions are erroneous, his views unsound, and are to be avoided. Yet the clinician endeavors to find the meaning of the lesion and of the disease process, and is in fact far more scientific than his friend the patho-anatomist.

Chapter XVII.

THE PATHOLOGICAL INSTITUTE AND PSYCHIATRY.

Pathological anatomy and bacteriology have an undue influence in moulding medical scientific thought and activity. This being the case medicine expects that scientific research in psychiatry should pursue the same channel, an absolutely profitless task. There is no use of deluding ourselves in the hope that we can make progress in the investigation of abnormal mental life under the guidance of pathological anatomy and bacteriology.

The finding of proximate causes does not explain insanity. I might as well say at once that this Institute was not built up on the plan of simply assembling these several branches of research and plunging into them blindly, describing facts without stopping to reflect on the general aim of the institution itself. Nor was it founded on the plan of using the mainstays of medical research, such as physiological chemistry, and particularly pathological anatomy, as the principal and guiding branches of research in psychiatry. Nor was it based on the plan of simply delving out any facts that research in these branches might unearth and expecting to hit, by happy chance, on some discovery of the *modus operandi* of abnormal mental life. No such plan was ever entertained.

The guidance of psychiatric research by the medical

conception of using anatomy, chemistry and bacteriology, would have been simple. We should merely have to follow the precedent of the pathological laboratory in medicine and extend it by adding chemistry and bacteriology. By focussing these sciences on autopsy material from the asylum or from hospitals of nervous diseases, recording the observations and then publishing them, side by side with the superficial clinical history, the task would have been finished and much "work" could have been put forth with that degree of celerity which the pressure for results demands from an institution of this kind before it can even become organized.

The medical conception of guiding psychiatric research by branches of investigation that do not in the least take account of the phenomena of mental life is utterly wrong. Had we, however, followed out this simple and fallacious plan of psychiatric investigation and poured forth observations of this character, it would have fulfilled the expectation of the medical conception of the research, met with approval, and the ordeal of trying to maintain a higher ideal could have been avoided. Meanwhile the psychiatrist, unless also influenced by the medical conception of the research, on observing this work might well remark: "This is the same old stuff only on a larger scale. The granules in the neuron are exceedingly fine and quite new. The chemical analyses of the excretions are more searching than formerly. The toxic factor in some forms of mental disease is more thoroughly verified. But through no stretch of sophistry am I able to find any approach to the explanation of the living phenomena—insanity itself. I still have no key to the solution of the general problem of abnormal mental life." On the other hand, if we adhere to the ideal of endeavoring

to furnish explanations of abnormal mental life and abandon the medical conception of psychiatric research, we run the risk of losing favor with the medical "ologists," such as the neurologist, pathologist, histologist, bacteriologist, etc., and perhaps with some psychiatrists, who under the influence of their medical training take the same narrow and fallacious view of psychiatric research.

In the midst of these difficulties, however, the choice is definite and clear. We are to follow out the true aim of science and to work out explanations, *theories* and *generalizations* of the abnormal phenomena of consciousness. To do this we cannot use the medical branches of pathological anatomy, physiological chemistry and bacteriology as the guiding sciences in our ideal of psychiatric investigation. These branches must be made entirely *secondary* and *auxiliary* to *general physiology*, *psychopathology* and *psychology*. I sincerely hope that we shall not be misjudged, if we have not brought forth various inco-ordinate observations on the dead tissues of the insane along purely medical lines of investigation, as though this could furnish any key to the understanding of living phenomena of abnormal mental life. We have desired to avoid this kind of work, unless it could *subserve some purpose in the explanation of insanity*.

I think it must be quite plain that, if we would ever find any key to the explanation of insanity, we had best first and foremost investigate the living phenomena of insanity and not by sciences which have to do with the third and fourth degree concomitants of abnormal phenomena of consciousness, such as anatomy and chemistry. If we wish to understand the *modus operandi* of insanity, let us by all means go directly to the fountain-head and give up the hopeless task of inductive ascent from the far distant

by-waters and remote side-channels of medical research. *We must study insanity itself,—we must examine, investigate and experiment on the living patient.*

Hitherto and even at the present time two obstacles have stood in the way of a direct psychopathological study of insanity. In the first place, a purely medical education does not only prepare one for the study of the abnormal phenomena of consciousness, but actually leads him astray. *Medical training leaves out psychology, the only science which can guide investigation of abnormal mental life*, and it is useless to try to substitute other sciences. In the second place, the difficulty of finding any well-grounded working hypothesis of insanity is further augmented by the fact that asylum cases are too advanced and far too greatly complicated to yield the key. What holds the science of psychiatry back is the fact of its being guided by medicine; it is a case of the blind leading the blind.

The plan of this Institute has been to make psychological groups of sciences the guide of psychiatric research. From the very beginning all our efforts were directed towards one aim,—the discovery of some general principle of abnormal mental life. The idea was to study the living phenomena of abnormal consciousness and find a working theory of the *modus operandi* of these phenomena. I think, if we wish to accomplish scientific work, the first thing to do is to survey the field by independent thought, and not be governed by too excessive a veneration for tradition, dogma and the formalism of the schools.

The first thing is to state the problem, to find out what is to be done. The second step is to find out how to solve the problem. The problem is the explanation

of abnormal phenomena of consciousness, the discovery of their laws. The way to solve the problem is very obviously by means of the sciences of consciousness, namely, psychology and psychopathology—and by this means alone. Start with this idea and you will be able to estimate the proper value of the medical branches of research in relation to psychiatry, and know how to use them. *In psychiatric research, especially when a working hypothesis is absolutely indispensable, medical sciences are to take second and not first place.*

The plan guiding the building of this Institute was to regard psychiatry as the keystone of the whole arch of sciences. Now psychology alone and by itself is inadequate; it needs the support and auxiliary work of other sciences. The psychological group of sciences is to furnish the guiding principle of abnormal mental life-history, a principle that should control and at the same time be verified by the researches of the medico-biological group of sciences. Given some key to the general *modus operandi* by psychological investigation of some very carefully selected psychopathological case, a case furnishing crucial tests, the work of the medico-biological group of the sciences becomes subject to control. We know where to direct it. We are then under the guidance of a general hypothesis of the phenomena of insanity, know what facts to *select* from the work of the medico-biological group and how to *use* them. It is only under such conditions that we are enabled to *make pathological anatomy of great value, because we can interpret its results in relation to the living phenomena*, and it is only under such conditions that pathological anatomy will cease to be a dead science and will become a really living science. Most assuredly, then, to find some foundation for psychiatric research, we must

begin at the living phenomena, find some key to their nature, and then only test and verify this theory by anatomy, chemistry and other sciences.

One can perceive that *the mainstay of this Institute is the field of the psychiatrist himself;* only we feel sure that at first we must begin in the investigation of abnormal mental phenomena outside of the hospital where they are less complicated. After some general key is found to explain these phenomena, the investigation may be extended little by little into the hospitals.

One point should be made quite distinct. *The plan and the motive inspiring the institution did not simply consist in assembling the various scientific departments under a common roof and bidding them work at the dead bodies of the insane.* Most assuredly not. This does not mean mutual co-operation of these sciences for the purpose of explaining the successions of the phenomena in abnormal mental life. The simple establishment of these departments in a common home does not mean *correlation* of the work toward a definite aim. All these departments might be established and although doing "work," giving forth "results," and industriously stimulating the same kind of activity in the hospitals, might leave us in the end not one whit nearer the laws and principles of abnormal phenomena of consciousness.

One might even add psychology to this group of sciences, and if one chooses the kind of scholastic "laboratory psychology" which is limited to the collection of statistical data of normal mental phenomena, such as reaction-time and the like, without in the least making a single step in advance. For the psychologist like other scientists falls into the notion that one is to be satisfied with collecting and cataloguing facts and data. Thus we

find that some psychologists while piling up many data concerning the psychophysics of sensation and perception, forget to make use of the facts or to work out theories to correlate the facts. Their work bears an analogous relation to the true aim of psychology as that of the histologist or patho-anatomist to the science of function. The pathological anatomist piles up facts of abnormal structure as though they were explanations of abnormal function, whereas only through the study of the latter can he expect to gain an explanation of his facts, and a guide to discriminate the non-essential from the essential in his particular study.

Normal psychology must speculate as well as observe, and to speculate safely it must study the abnormal. If a department along the lines of simple "laboratory" psychology be added to the previous medico-biological group, the plan for psychiatric research would seem quite perfect. The delusion would indeed be quite strong. Psychology would then be working with the medico-biological group. The only trouble is that a psychology of numbers and incoherent "facts" by merely recording data and measurements can hardly give us a clew to the explanation of abnormal mental life. Collections of reaction-times among the insane and voluminous records of psychophysical measurements do not explain the abnormal phenomena of consciousness. Such a plan, even with the experimental type of psychological research included, might remain a *collection* but not an *organized correlation* of sciences in psychiatric research. Such a type of psychological research cannot possibly guide the work of the other sciences and the whole institution would fall short of its avowed purpose—the formulation of laws and principles of the phenomena of insanity.

In the amount of "work" related to insanity, however, that might be brought out of such an institution, its ultimate aim of explaining the living phenomena in insanity might be lost track of for some time. The example of such an institution would be pernicious. It would encourage others to fall into routine work and strongly discourage and delay the attempt to lead psychiatric research from the dominance of fact-collecting into the channel of the higher aim of elaborating the laws of mental life. The key to the finding of these laws lies in the domain of abnormal consciousness, not that the phenomena are at all different from the normal, but they better exhibit the phenomena of progressive dissociation. This furnishes the key.

I have desired to avoid turning psychiatric research into a cataloguing of facts in this institution, either under the guidance of pathological anatomy or of "laboratory psychology." On the grounds of expediency, however, it often seemed almost compulsory, from the pressure of bringing forth immediate results under the dominance of the mistaken medical idea of psychiatric research, to postpone the fulfillment of the ideal of this Institute and give over its energies to pathological anatomy and describe ganglion cell lesions wherever they could be found in the asylum mortuary and report it in the journals. The clinical histories could be written side by side with the morphological account, the interrelation of the two, the vital problem could be left for someone else to work out. I think, though, to relinquish the chosen aim of the research, even temporarily, for the sake of satisfying this mistaken notion for results, would have been dangerous. Had we started in this fashion, even holding in mind the ultimate aim of finding some working hypothesis of insanity to guide observation, it is quite likely that this aim would have

been indefinitely postponed, and that we could have hardly paused long enough to work out the true aim of our endeavor. For the research is not isolated in this Institute; it extends out into twelve great hospitals with some twenty thousand patients and among one hundred to one hundred and twenty of our colleagues forming the staffs of these hospitals. It may be seen that the extent of the work of this Institute is rather extensive. I think it would be wrong to start right off simultaneously throughout these hospitals and deflect the work blindly into the channel of pathological anatomy and stop at the recording of the facts or with deductions so narrow as to be useless. It would be an unworthy response to so great an opportunity.

All over the civilized globe laboratory workers seem most actively engaged in recording observations gained by the Nissl method, although a good part of this activity seems to be conducted at the expense of reflections on the meaning of the observations. Such work by no means constitutes the central inspiration and motive of an institution for psychiatric research. We have to find a guide for this work and make it subserve some purpose in explaining the phenomena of insanity, or to show how these changes are effects of the morbid process concomitant with abnormal mental life. Work of this kind, and everything else, must not interfere with the proper aim of such an institution.

Although two years is an exceedingly short space of time, a wide range of cytological investigation of the neuron has been conducted more or less successfully. This morphological work embraces studies in the histogenesis of the neuron, in its comparative cytology through quite a number of invertebrates and lower

vertebrates, and in many and varied pathological conditions in man, also experimentally induced in animals. All this work was not rushed into print as a mass of facts under the delusion that it explains the phenomena of insanity. These observations have, in the first place, been *used* for the formation of a general theory of the phenomena of insanity, and, secondly, *they have been used to lend support to the theory of neuron energy*, and, finally, the facts have been used to explain, as it seems to us, the mechanism of certain phases of mental and nervous disease process. Thus an explanation was found of peripheral neuritis, tabes, general paresis, and of a large part of the system diseases of the spinal cord and brain, such as combined sclerosis, amyotrophic lateral sclerosis, Landry's paralysis, pernicious anæmia, sclerosis, and of a large part of the whole problem of fibre death in the nervous system. *This has been accomplished by working out the significance of the migration of the neuron nucleus and the excretion of the metaplasm particles.**

Chapter XVIII.

Medicine and Psychiatry.

I have spoken somewhat freely of the pressure for results and its bad influence on the growth of a young institution, with the risk of having it fall amiss all around, both to the physician and the psychiatrist. If it concerned this Institute only it would certainly not be said, it would be a most unhappy return for the magnificent opportunity granted us by the directors of the hospitals and our Commission in Lunacy. If, however, this pressure for premature results is liable to depress and pervert

* An account of this work will appear in a future number of the Archives of Neurology and Psychopathology.

the progress of the science of psychiatry in general, it becomes a very serious matter and demands consideration.

In medicine there are an enormous number of eager, active "workers" in hundreds of laboratories vying with each other in the accomplishment of mechanical desk work on dead tissues. Every university has them—their name is legion. A new dye, a new technical method is a boon to them, it opens a new field for more "work." The cause of the phenomena is neglected, the process of transition of cause into effect dwindles out of sight. By its very volume and momentum, by the force of example, the influence of all this laboratory "work" widens and deepens the stress to conform to it.

The principal cause of this unintelligent vain labor and travail is our unfortunate manner of medical education. It is the fault of those who teach medicine. We fail to give our students so much as an inkling into the philosophy of medicine; we lead them to believe that the great goal of good work is the noting down of details. Observation of details is indeed necessary, but reflection and the use of the methods of seeking after causes are as much requisite, and possibly far more indispensable. The result is that too many men leave the medical university without knowing what science really means. They are possessed of the idea that science consists solely in observation of desultory facts and in aimless experimentation, and they consequently avoid the philosophy of science like a pest. They become ingrained with that false and mischievous notion that success is best achieved by sticking to one thing, one highly particularized line of observation.

The natural result of this training is that when men leave college and wish to enter the science of medicine,

they go where desultory observation of new things has the greatest opportunity—pathological anatomy and bacteriology. They become skilful with technical methods and labor with the sense organs at laboratory desks despising all mental activity. The banishment of reflection is with them the *sine qua non* of good scientific work. To make an attempt to understand the phenomena and form a hypothesis, then verify it and arrive at a theory is a sacrilege. Reflection is theorizing, metaphysics, or as some of the profession like to express themselves strongly in popular parlance, mere rot. Their conception of the aim of science would have been pitiable, had it not been so ludicrous; science, according to them, is a kind of dime museum where all sorts of odd things and new curiosities are to be collected for exhibition.

It would be absurd to think for a moment that facts are of no value in science—science must have facts, but they are relatively useless until we can give them a valuation by the methods of reasoning. Without training in the general principles of biology, general physiology and psychology, we can hardly expect the medical student to find the basis for any broad elaboration of facts. Many brilliant minds in this field do not lead their energies toward the higher motives of science, because of their training in medicine and the lack of correlation with other sciences. Thus, year by year, the army of "workers" grows and the influence of joining it becomes stronger by mere force of social suggestion and imitation. Let a man leave the work desk in the laboratory to reflect on a purpose for his work, to subordinate the aimless observation, mechanical experimentation to an idea, to formulate a problem, and straightway he is a deserter from the ranks and is branded as an "ideal" idler, as a metaphysician. So great is the

conceit of these "workers," so narrow is their mental horizon that outside their field of occupation everything is regarded with an air of superiority and utter contempt. Thus to one of this type of "workers" a book was shown in manuscript form. He looked at it with great arrogance and asked: Anything about the Nissl stain? No. Then it must be metaphysics. When Egypt was conquered by the barbaric Arabs the problem was what to do with the great Alexandrian library. Is the Koran in it? the barbarian asked. No. Is it in the Koran? No. Then it is useless stuff; burn it! I do not know whether the laboratory patho-anatomists are direct descendants of those barbarians, but they are certainly their successors in spirit.

Another spur to the haste to record desultory scrappy descriptions of facts is the great number of journals in medicine. In medical science there must be at least six or seven hundred journals. This is about five times as many as any other science uses, and about five times as many as necessary for well considered, deliberate and valuable scientific contributions. The rest are too much in the nature of catalogues, and to search through them to find the occasional papers of value is indeed a task. The evil is happily overcome by the year books; although one often hears the exceedingly valuable work of those who cast out the chaff in the year books pitied by the "workers" as compilers. I think the service rendered to science by those who assemble these disjointed fragmentary descriptions in some succession and order, is as valuable, if not more so, than many of the contributions from the "workers."

Such unnecessary journals play no inconsiderable share in urging medical men to forget the true aim of science

in the blind, feverish race for "facts." Every centre of research, every laboratory, seems to desire to individualize its work in a new journal. Before long it is quite liable to happen that the work has to be made to order to keep the journal going. The work has to be ground out on time. This is simply ruinous to the higher motive of science. One should think twice before starting a new medical journal, that is, if it purports to advance the science of medicine. If a journal is inaugurated, it is well to show its purpose, as Roux has done in the fine introduction to his journal.

It is unnecessary to allude to the similar baleful influence exerted by superfluous medical societies in spurring medical men along hasty mechanical lines of work. The effect of it all, however, whether from one direction or another, is to drive medical research into a beaten track. Medicine, headed by pathological anatomy and bacteriology, is becoming too much a school of desultory facts. In America, we are trying to drive science along with the same haste that is characteristic of activity in other walks of life. No sooner is a scientific institution inaugurated than results are immediately demanded. The task of conforming to this demand has been particularly hard in this Institute, for it had no precedent to follow; it had to plan out all of the work on an entirely new basis. Haste is the bane of scientific *research.*

In the pressure to bring out work, problems whereby work can be guided intelligently, problems anticipating the *renaissance* of psychiatry as a science have to be ruthlessly cast aside. An institute devoted to the science of psychiatry is like an organism, it must grow and develop, it cannot become great by the irrational demand of the "workers" in medicine to make hasty "work."

Medical training thwarts all endeavors to find a pathway for the progress of the science of psychiatry. Investigations in psychiatry are to follow the pattern of medical laboratory work, and that unless indulged in it all research is deemed a failure. If we have come to such a pass, it is indeed time to declare openly that medicine is no guide for the student of psychiatry.

Neurologists, pathologists, histologists and all those high sounding "ologists" think that they can afford to disdain, deride and even to slander and defame the psychiatrist and his science. As a matter of fact the investigator of abnormal consciousness, with his broad view of life and science, has certainly a larger horizon and wider scope for scientific thought. It is high time that the psychiatrist should free himself from the incubi and succubi, the medical "ologists," that have weighed on him for so long a time. In the *art* of psychiatry medicine has been and still is a great mentor; in the *science* of psychiatry medicine can only lead astray.

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at some length. Thus we find in such descriptions the terms, granular and cloudy swelling; pigment degeneration; vacuolation; colloid degeneration; shrinkage; loss of nucleus, nucleolus, and processes; increased or diminished staining capacity; rupture of cell body and processes; dilatation of pericellular lymph spaces, and infiltration of this space and of the cell body with small round cells. Based upon the observation of these grosser changes the knowledge of the pathology of the ganglion cell had been very widely extended, and successfully applied in the interpretation of morbid clinical phenomena.

Yet in spite of the prodigious labor steadily devoted to the subject, it cannot be claimed that any systematic basis for the classification of pathological changes in ganglion cells had been elaborated. In fact it had never been determined whether many of the changes described were the result of vital or of cadaveric processes, while it was constantly acknowledged that the described alterations were probably preceded by less marked changes not then demonstrable.

Further, it had long been apparent that existing technical methods failed to reveal a whole series of more delicate cytological changes which must be supposed to result from the action of powerful nerve poisons, in acute intoxications and in diseases proving rapidly fatal with pronounced nervous symptoms. The histological structure of the ganglion cell was practically inaccessible to the investigator, equipped with the ordinary methods for microscopical examination of tissues.

The past decade, however, has witnessed the development of a method of cytological research which has greatly enlarged our conceptions of the structure of nerve cells, and is claimed to demonstrate those finer alterations of

structure which have been obliterated by other technical procedures.

To determine to some extent how far these claims are justified, to ascertain in what these finer cellular alterations consist, and what significance may be attached to their presence, have been the objects of the present study which has occupied the writer during the past two and one-half years. Incidentally, the results bear on the relation of the nervous system to general diseases. The work has consisted in the examination of the nervous system in various diseases, by means of Nissl's and related methods, and in some experimental studies. The full report of these studies necessitates a review of the present status of our knowledge of this method of cytological research and of the cellular changes which it demonstrates.

Section I.

TECHNICS.

In 1885 Nissl[1] called attention to the fact that chromium salts destroy the finer structure of nerve cells, while preserving the fibres, and that if we are to demonstrate the minute structure of the cell, other hardening agents must be used. For this purpose he recommended alcohol as a fixative fluid and magenta red, dahlia, and vesuvin as staining agents. The sections of the tissues thus hardened were to be heated moderately in any of the above dyes, decolorized in alcohol and anilin oil, cleared in benzine, and mounted in balsam. By careful comparison of normal and pathological brains, Nissl claimed to demonstrate pathological changes in the cortical nerve cells which had hitherto escaped detection.

In 1890[2] Nissl recommended the use of methylene blue in watery solution instead of the dyes formerly employed.

Methylene blue had already been extensively used in blood technics by Ehrlich, and had been applied by him in 1886 in the form of intravenous injections to demonstrate some of the finer details of the structure of nerve cells and especially of nerve end-organs.[4]

From what we now know of the great variety of appearances presented by the anterior horn cells of the spinal cord in disease, it is not a matter of surprise that the early experience with this method led to much confusion. All grades of intensity of stain and apparent change in structure were met with under apparently identical conditions, and seemed to be referable to imperfections in the new method. Chromatophilic cells were found side by side with chromatophobic cells, and in some regions all the cells might appear chromatophilic, or, again, chromatophobic. It was hoped to avoid some of these irregularities by improvements in fixation and staining and in 1894[3] Nissl published a very complex procedure for the staining by methylene blue. The tissues, not longer than twenty hours *post-mortem*, were to be hardened in 96 per cent alcohol, and sectioned without being embedded in celloidin. To the methylene blue solution (3.75 parts per 1000 of distil. water) was added, at the suggestion of Frank, of Wiesbaden, 1.75 parts of Venetian soap, and in this solution the section was heated until bubbles were produced. They were then decolorized in anilin alcohol, (anilin oil 10, alcohol (96 per cent) 90), until the dye ceased to be extracted. They were then placed upon a glass slide, dried by blotting paper, treated with a few drops of oil cajeput, dried again, finally treated with a few drops of benzine, mounted in benzine colophonium and heated till all benzine was driven off. The benzine colophonium was made by dissolving colophonium in a

sufficient amount of benzine and allowing the fluid to settle for 24 hours, when the supernatant portion became translucent.

The rationale of this method has not, so far as the writer is aware, been set forth in any of Nissl's publications. All of these modifications of the original method, especially the addition of an alkali in the form of soap, tend to give clearer differentiation of the chromatic bodies, while the above mounting medium was probably devised to prevent the fading commonly observed soon after mounting sections in balsam.

In the hands of various investigators the original and perfected method of Nissl has been submitted to several modifications.

Rehm[5] recommends immediate fixation in strong alcohol as the most generally applicable method for nervous tissues allowing by different staining methods the demonstration of cellular and nuclear structure as well as of fibres. Decolorization in anilin alcohol he finds necessary only in old specimens in which it clears up the deeply blue stained globules of free myelin. In other cases he prefers strong alcohol which in his hands seem to give better differentiation between nerve and connective tissue cells, the former remaining dark blue, the latter assuming a greenish tinge after staining in methylene blue. For the complete differentiation of nerve and neuroglia cells he urges the use of a counterstain, viz.: 1 per cent alc. sol. of fuchsin, in which specimens remain fifteen minutes. The use of some similar acid counterstain has also the advantage of demonstrating the achromatic substance of the cell body.

Lenhossek[6] has secured satisfactory results by hardening specimens in 20 per cent formalin, followed by strong

alcohol. He prefers oil of cajeput as a clearing medium. Staining for five minutes without heat in a concentrated solution of thionin he has found to give very excellent results. Sections thus stained are to be washed in water, decolorized in anilin alcohol, cleared in oil of cajeput, passed rapidly through xylol, and mounted in damarlack or in balsam. He has also secured good demonstrations of chromatic bodies by the use of saffranin, fuchsin, dahlia, and ordinary Bohmer's hematoxylin.

During the past three or four years much of the reported study of Nissl's stain has been made on tissues hardened by corrosive sublimate. This chemical has been used as a saturated sol. in water or in .6 per cent salt sol., or in the form of Lang's fluid: mercuric chlor., 5 grms.; sodium chlor., 6 grms; acetic acid, 5 grms.; aq., 100 grms. All of these solutions have been reported as furnishing very excellent results in cytological detail, and they have been claimed in some instances to have proven superior to alcohol. Flemming[7] who actively supports the fibrillar theory of the structure of ganglion cells, hardens the tissues in sublimate and stains with Delafield's or Heidenhain's iron hematoxylin. Colucci[8] obtains very handsome specimens by hardening in ½ per cent picric acid in water or in alcohol, or in picric acid and sublimate.

Held[9] secures very instructive pictures of the ganglion cells by staining with erythosin and methylene blue. The method is as follows: The specimens are fixed by preference in Van Gehuchten's solution. Alcohol abs., 60; chloroform, 30; ac. glac., 10; or in the following sol.: Sublimate, 1; acetone, 40; aq., 100. The sections are first stained in erythosin, 1; aq. dist., 150; ac., 2 gtt.; which is gently warmed one to two minutes. They are then washed in water and stained in a special sol. of

methylene blue, composed of Nissl's fluid (usual formula) and 5 per cent watery sol. of acetone, each equal parts. In this dye they are warmed till the odor of acetone disappears, then decolorized in $\frac{1}{10}$ per cent sol. of alum till the sections are red; washed in water, dehydrated in alcohol, and cleared in oil of cajeput. By this method the body of the cell appears red, the chromatic masses blue; nuclear membrane red, nucleolus blue, secondary nucleoli violet.

Savdovsky[10] expresses preference for a modification of Nissl's method devised by himself. The specimens are hardened three days in 10 per cent formalin, followed by alcohol. The sections are stained 15 to 60 seconds in 1 per cent sol. methylene blue, or better in a sat. sol. of fuschin in 5 per cent carbolic acid. They are decolorized in 1 per cent acetic acid till the gray and white matter appear differentiated, and finally dehydrated in absolute alcohol.

Smirnoff[11] hardens the tissues in alcohol as usual, but stains 10 minutes to 24 hours in a solution of toluidine blue, 1 part, NaCl .75, water 98, decolorizing in sat. alcoholic solution of eosin, thereby staining the achromatic part of the cell body.

Marina[12] recommends the following mixture as a fixative for nervous tissues. Alcohol 96 per cent, 100 cc.; formol, 5 cc.; chromic acid, 10 cgm. The tissues should remain in this fluid, frequently renewed, for about one week, after which either Nissl's or Weigert's staining methods may be successfully applied.

Graf[13] recommends as a specially valuable fixative for cytological study, mixtures in equal parts of sat. sol. of picric acid in water, and of formalin 5, 10, or 15 per cent. In these fluids specimens should remain from one-half to two hours and then be washed and thoroughly hardened

in alcohols 30–98 per cent. As stains he prefers Heidenhain's iron hematoxylin and Bordeaux red. For the demonstration of fibrillar structure Graf recommends the following mixture: 4 vols. oxalic acid (8 per cent); 3 vols. alcohol (95 per cent); 3 vols. chromic acid, (1 per cent). In this fluid thin pieces of tissue should remain one-half to two hours, after which they are washed in water and alcohol. The sections are to be stained in iron-hematoxylin.

Cox[14] recommends the following mixtures for the demonstration of the fibrils as well as of the chromatic bodies of ganglion cells:

(1)	Sublimate, sat. watery sol.	30	
	Osmic acid, 1 per cent	10	
	Acetic acid (glac.)	5	or
(2)	Sublimate, sat. watery sol.	15	
	Platinic chloride, 5 per cent	15	
	Osmic acid	10	
	Acetic-glac.	5	or
(3)	Sublimate, (sat. watery sol.)	30	
	Formalin,	10	
	Acetic acid, glac.	5	

Specimens should remain in these fluids two to three days and be washed in 60 per cent alcohol. Sections may be stained in Delafield's hematoxylin, by Heidenhain's iron hematoxylin, or by a process specially devised by this author, of which details may be found in the original article.

As a decolorizing fluid, Gothard[15] recommends on various grounds the following mixture, which dissolves celloidin, decolorizes the achromatic substance perfectly,

and sharply differentiates the chromatic structure: Creosote, 50 cc.; oil of cajeput, 40; xylol, 50; absolute alcohol, 160.

Rossalimo and Murawjeff,[16] recommend fixation in formalin both for Nissl's stain and for the demonstration of degenerative products of myelin. They prefer a 2–3 per cent solution for the first two days, replacing this with a 4 per cent sol. in which the tissues may remain indefinitely, to be transferred at leisure to alcohol for complete hardening and embedding.

In addition to many of the fixing agents thus far enumerated the writer has had satisfactory results from the use of a 5 per cent solution of formalin saturated with bichloride. The addition of formalin greatly accelerates the penetration of bichloride, this mixture being quite as active in this respect as Lang's fluid.

After the use of mixtures containing formalin, the cells will be found to stain darker than usual, and to require rather longer decolorization in alcohol. In specimens fixed by this agent, the chromatic network of the small cortical cells appears more distinct than after fixation by most other methods, and the usual tendency to fade has been entirely lacking in specimens now a year old. These effects may all be referable to the distinct action of formalin as a mordant for basic dyes.

Formalin alone in 10 per cent sol. has given very excellent results in the writer's experience. This fluid penetrates with considerable rapidity, and shrinkage of the cell from subsequent hardening in alcohol has been almost entirely lacking. Thin sections are necessary when examining tissues hardened by this agent.

In most of the later cases in the present series, Van Gehuchten's fluid was the hardening agent employed;

(absolute alcohol, 60; glac. acetic, 10; chloroform, 30); and the results were usually satisfactory. There are, however, objections to the use of such an acid as glacial acetic in the study of nerve cells, as this chemical penetrates in advance of the other ingredients of the mixture, and when used alone transforms nervous tissue into a swollen, gelatinous mass.

A very short experience in the use of Nissl's stain furnishes convincing evidence that this field of pathological research is largely a study of microscopical technics. The almost infinite variety of appearances presented by nerve cells treated by this method and its modifications, has left the subject, even after the labors of a decade, in a state of considerable confusion. We meet on the one hand with the denial by Trezebinski,[17] Kronthal,[18] Fisher,[19] Held,[9] and others that the chromatic masses, the principal element demonstrated by Nissl's method, exist as such in the living cell, these investigators claiming that they are the artificial products of fixative agents and cannot be seen in fresh specimens or in frozen sections. Held furnishes apparently undeniable proof that the minute structure of the chromatic bodies may be altered at will by varying the strength of the alcohol in which the tissues are fixed, and the same writer finds that chromic acid in 2 per cent solution precipitates the chromatic substance in finely granular condition, and in 1 per cent solution causes it to appear nearly homogeneous, while a solution of ammonium bichromate leaves it entirely homogeneous.

These and similar observations indicate merely that the chromatic substance exists in the cell in fluid form, and while we are dealing in the hardened section with an arti-

fact, it seems probable that it is an artifact that under uniform conditions will give a uniform appearance. It does not seem, therefore, to be a matter of prime importance in the choice of a fixative agent, whether it fixes the chromatic substance in fine or coarse granules or in a homogeneous mass.

A much more difficult question in technics is encountered in the diffuse dark blue stain presented by many cells after treatment with methylene blue and denominated by Nissl "*the chromatophilic condition.*" It has been claimed by Flesch and Koneff[20] that this quality is a normal character of the cell, indicating a distinct physiological condition. Nissl[21] very early and rightly, as it seems, concluded that this character is artificial, and is devoid of pathological significance, resulting from accidental and as yet undetermined effects of hardening agents or from post mortem change. In the writer's specimens prepared after hardening in Lang's fluid the chromatophilic cells were found in greater numbers than in those tissues hardened in alcohol, especially in the outer zones of the blocks of tissue. On various grounds it seemed probable that the acetic acid in Lang's fluid, which penetrates in advance of the bichloride, might be responsible for this peculiarity—a suspicion which was proved to be at least partially correct by the following experiment. A small segment of the medulla of a fresh case was subjected for 24 hours to the action of a 5 per cent sol. of acetic acid. as found in the composition of Lang's fluid, it was then hardened in alcohol, and sections 15 μ in thickness were stained in the usual way. The cells without exception were found stained darkly and diffusely blue, separate chromatic bodies being distinguishable in a very few instances only. An adjoining segment from the same

medulla hardened in alcohol gave very few chromatophilic cells. The writer, therefore, discarded the use of Lang's fluid as a fixative agent on account of the disturbing action of acetic acid. Incidentally, the result stands at variance with the statement that immersion in weak acids dissolves the chromatic bodies as reported by Eve,[22] whose experiments, however, were conducted on sympathetic ganglion cells.

The chromatophilic condition is however too frequent in occurrence and too irregular in distribution to be always referable to a uniform cause, such as the action of fixatives. Not rarely a markedly chromatophilic cell may be seen immediately adjoining a perfectly normal cell, and such a combination is difficult to understand, on the theory of irregular penetration of fixative agents or from the action of any abnormal chemical agent spontaneously produced in the tissue after death.

In the study of post mortem and putrefactive changes, to be considered later, the writer finds no evidence that the chromatophilic condition may result from such processes. In fact, in fresh nerve tissues smeared, dried and stained on a glass slide, distinctly chromatophilic cells may be found. Turner,[23] has also seen them in fresh specimens examined in Farrant's solution and stained with methylene blue.

From a study of the conditions under which these chromatophilic, perfectly opaque and homogeneous cells are found, the writer has been convinced that two principal factors are responsible for their production: (1) If the entire thickness of an ordinary section (15—20 μ) is occupied by a compact normal cell, which is imperfectly decolorized, that cell may appear homogeneous and very darkly stained. For the majority of cells seen in any

particular section of tissue do not extend throughout the section, and it is usually possible to find in every section, no matter what its thickness, some portions of cells which are excessively thin and clear, while others are very dark. (2) When the chromatic bodies have been uniformly and minutely subdivided, it may be impossible, even in comparatively thin sections, to detect these resulting granules and the cell if fully stained, and especially if somewhat shrunken, may appear very dark and homogeneous. The writer has rarely encountered distinct examples of the chromatophilic state which could not be referred to one or both of the above conditions. (Cf. Heimann, loc. cit. p. 319) Kreyssig,[24] Trezebinski,[17] and Nissl,[21] have noted that as a rule the chromatophilic cells are much shrunken, leaving wide pericellular lymphatic spaces.

The *formation of vacuoles* has long been recognized as one of the necessary imperfections in most methods of fixation of nerve cells. Kreyssig,[24] observed vacuoles in the majority of normal ganglion cells preserved in Mueller's fluid. From observations of Trezebinski[17] and others it appears that vacuolation is more frequent after hardening in chromium salts than with other fixatives, but its occurrence in normal specimens after fixation in alcohol and bichloride has been repeatedly noted. Yet vacuolization in any marked degree is regarded by most authorities as of distinct pathological significance. The complete absence of vacuoles has been noted in ganglion cells examined in the fresh condition by Kreyssig,[24] Trezebinski,[17] and Held,[9] with whose observations the writer's experience accords. Held very graphically describes and depicts their formation in fresh ganglion cells on the addition of water to the crushed

tissues. He finds that fine vacuoles first appear in and about the chromatic bodies, that they swell markedly on the addition of water, and that their size and contour in hardened specimens varies much with the different fixatives.

The writer cannot agree with the statement often seen that vacuolation may be regarded as pathological only when it is found in advanced degree. Among the present cases, extreme vacuolation when found, was always plainly referable to post-mortem processes. The study of cadaveric changes in ganglion cells indicates that vacuoles are one of the most constant of post-mortem products; and that they frequently form in considerable numbers and of large size within a few hours, often preceding other post-mortem changes. Especially when the brain and meninges are œdematous, or when the patient has suffered from general sepsis, vacuolation of cells may be expected unless the tissues are fixed very shortly (one-half hr.) after death. The above observations, as well as the circumstances under which vacuoles are usually found in stained specimens, indicate that in the great majority of instances vacuolation of ganglion cells is a cadaveric or artificial product, and in any case with the present state of our knowledge is devoid of definite pathological significance.

The practical indications for the avoidance of this artifact are, then, the rapid fixation of material as fresh as possible, by means of a rapidly penetrating fluid of high osmotic power. A saturated solution of bichloride in normal salt solution recommends itself for this purpose and in the writer's hands has given results very little disturbed by vacuolation, but its slow penetration requires that thin pieces of tissue only should be used. Formalin is also very reliable in this respect.

Under many conditions, the nucleoli of ganglion cells presents spherical transparent globules often projecting from the edges of the nucleolus and frequently spoken of as *nucleolar vacuoles*. It is doubtful if these appearances are to be regarded as of similar character with the vacuoles of the cytoplasm. It appears more probable that they represent subdivided portions of the acidophile substance normally found at the centre of the nucleolus. This appearance of the nucleolus was observed in some degree in all the cases of the present series, but the irregularity of its occurrence has made it impossible to draw any conclusions as to its real nature and significance.

The shrinkage caused by strong alcohol is one of the chief objections to its use in the Nissl method. Many of the instances of the chromatophilic condition are doubtless referable to this action. The appearance of large pericellular lymph spaces about irregularly shrunken cells and of peculiar folds in the nuclear membrane are nearly constant artifacts resulting from this method of fixation. So constant is this result that Lenhossek,[60] was led to believe in the normal existence of a considerable free space about the spinal ganglion cell, an artifact which he now largely avoids by perfect fixation of fresh specimens in sublimate 1; acetic 40; aq. 100, as previously adopted by Flemming. This fluid may, therefore, be recommended as a fixative in this respect. One of the chief advantages of formalin as a fixative is the usual absence of shrunken cells in tissues hardened in this agent.

Besides the examination of stained sections of hardened tissues, other methods of study deserve notice in this connection. 1st. The staining of living nerve cells by the intravenous injection of methylene blue as introduced by Ehrlich,[4] has demonstrated some of the finer details of

the fibrillar structure of sympathetic nerve cells and of terminal end-organs, and the results of this method have important influence on the views now held as to the significance of the chromatic bodies demonstrated by other methods. 2d. The study of fresh portions of nervous tissue crushed under a cover glass and stained by methylene blue as practiced by Thanhofer,[25] Kronthal,[18] Held,[9] Turner,[23] and others, or spread on a slide, dried by heat, or teased in salt solution, has proven of similar import. Arnold[26] macerates small pieces of the gray matter for 2 to 24 hours in 10 per cent sol. of K. I. to which a few drops of Tr. Iodine are added, and examines the fresh specimens stained by eosin. 3d. The pictures furnished by frozen sections stained without the action of any fixative agent cannot be ignored in discussing the structure of the living nerve cell.

By far the clearest demonstration of the cyto-reticulum, of the relation of the so-called achromatic and chromatic structures of the cell, and of the structure of dendrites, secured by the writer, has been obtained in freshly and finely teased specimens of gray matter, fixed by heat and stained by methylene blue and erythrosin. This method cannot, however, be recommended for general purposes, as the large majority of cells are destroyed and the thicker portions of the cells, especially the perinuclear region, are usually found very dense and obscure.

Summary.

Fixation.—To summarize the observation on technics it may be said that alcohol 95 per cent to 97 per cent is most generally used as a fixative. Its superiority consists in its convenience and the compact appearance of the chromatic structures which it insures. Its great disadvantages are

the shrinkage of cells, which is usually very annoying, and its comparatively slow penetration.

The writer believes that a saturated solution of bichloride of mercury in .6 per cent salt sol. is superior to alcohol for many of the purposes of Nissl's stain, and that a saturated solution of bichloride in 5 per cent formalin (or more) is superior for the demonstration of the chromatic network.

Van Gehuchten's fluid, absolute alcohol, 60; chloroform, 30; ac., 10, is to be recommended for the study of a fibrillar structure of the cell.

The writer is at present using formalin 10 per cent as the initial hardening agent. Its results with Nissl's stain are good, and Weigert's staining method may also be employed after such hardening, but not always with success.

The fluid recommended by Marina,[12] alcohol 96, 100 cc.; formalin, 5 cc.; chromic acid, 10 cgm., deserves trial, as it is said to permit of the use of several staining methods.

More important than the choice of any particular fixative is the care in handling the tissues, and the exclusive dependence upon thin pieces of tissue, 1—2 mm., which can be rapidly penetrated by all agents.

Embedding.—Very thin sections, 1 μ, must be cut in paraffin. Properly hardened tissues may be cut 3—5 μ, in celloidin, which is quite thin enough for most purposes. For permanent preservation, tissues embedded in paraffin are superior.

Staining.—The writer has been unable to find any advantage in the addition of soap or any other alkali to the simple 1 per cent solution of methylene blue in water; nor do any of the related dyes possess distinct advantage

over methylene blue. In decolorizing it is important that the alcohol last used should be entirely free from dissolved methylene blue. There appears to be no distinct advantage in the addition of anilin oil to the decolorizer. Erythrosin is superior to eosin as a counter-stain and should be used after the method devised by Held and previously described. Heidenhain's hematoxylin is to be recommended for the demonstration of the fibrillar structure of the cell.

Oil of cajeput gives clearer demonstration of the chromatic structures than any other clearing agent. Specimens hardened in fluids free from acids, cleared in this oil, and mounted in Canada balsam, do not fade seriously, at least within two years.

Section II.

HISTOLOGY.

The Structure of the Chromatic Substance.

The employment of Nissl's stain at once greatly enlarged the knowledge of the histology of the ganglion cells, and although the chromatic bodies had been previously seen and described by Flemming[27] in 1882 and were remarked simultaneously by Benda[28] and Nissl[1] in 1885, it was entirely owing to the excellence of the technical methods devised by Nissl that this investigator was enabled in a comparatively short time to propose a new classification of nerve cells based upon the character of their chromatic substances.

Nissl[29] divides all nerve cells into two main divisions: 1st. The small ganglion cells, *karyochromes*, of which the distinguishing characters and basic staining elements are

to be found in the nucleus. 2d. The larger cells, *somatochromes*, of which the distinguishing characters and chromatic substances are to be found in the body of the cell.

In the first division he distinguishes: 1st, as *karyochromes*, those cells containing a small amount of chromatic substance about a rather small nucleus, as in the cells of the *substantia gelatinosa of Rolando*, and 2d, as *cytochromes* those cells whose nuclei never exceed in size the nuclei of neuroglia cells, as in the cells of the granular layer of the cerebellum.

In the 2d division, *somatochromes*, are the majority of ganglionic cells, whose distinguishing characters are found in the chromatic substance of the cell body, and of which four main groups may be distinguished.

1st. *Archyochromes* (*archos*, network) in which the chromatic substance is found about the nucleus in the form of a fine network, often producing a longitudinal striation, as in the pyramidal cells of the cerebral cortex.

2d. *Stichochromes* (*stichos*, spindle) in which the chromatic substance is found as a series of lenticular spindles or masses composed of fine granules arranged parallel to cellular and nuclear borders, as in the anterior horn cells of the spinal cord.

3d. *Archystichochromes*, of which the body shows a combination of the structures of the two preceding varieties, as do the cells of Purkinje.

4th. *Gryochromes* (*gru*, granule) in which the chromatic element is in the form of granules irregularly placed throughout the cell body, but usually forming threads or heaps, as in the cells of the *corp. striatum*.

All types of cells may show variations in the quantity and compactness of the chromatic substance. Those in

which the chromatic bodies stain intensely with methylene blue are indicated as *pyknomorphous*; those which stain faintly, *apyknomorphous;* while the intermediate grades are denominated as *parapyknomorphous*.

In the *chromatophilic condition* the cell appears shrunken, intensely stained and almost homogeneous, the outlines of nuclei and chromatic bodies being faintly or not at all visible. This condition Nissl regards in all cases an artifact.

The classification of Nissl was proposed merely as a provisional plan for the description of ganglion cells and in spite of many practical and theoretical objections to it, has been widely adopted as a temporary convenience.

The objection most powerfully urged against such an early attempt at classification is the fact that in only two types of cells has the finer structure been thoroughly investigated by this and complemental methods—namely the anterior horn cells of the spinal cord, and the cells of the posterior spinal ganglia.

Benda[30] urges against this classification the lack of purity in the type of cells, finding many transition forms between the various groups of Nissl and more reasonably the supposition that the chromatic masses are not preformed elements of the cell but depend in form upon other fixed constituents of the cytoplasm.

These and other similar considerations have, however, proved inadequate criticisms against a classification based upon very distinct grosser morphological differences.

The further attempt of Nissl[34] to connect the various morphological characters of the cell with distinct physiological functions has been much less successful. In only one group of cells, the stichochromes of the anterior horn of the spinal cord and medulla, does it seem probable

that a distinct function is indicated by a particular type of cell, and as the question is summarized by Van Gehuchten,[31] the facts at present, while not in opposition to this view, are quite insufficient to be convincing. Van Gehuchten admits that the same type of cell under like conditions always presents the same structure, as in the cells of origin of all peripheral motor nerves, the cells of the spinal ganglia, the olfactory bulb, the *cornu ammonis*, etc.

Colucci,[32] distrusts this particular claim of Nissl on the general ground that the data are too few to warrant a classification based on one peculiarity of the cell, while ignoring its features demonstrable by other methods, such as that of Golgi.

Lenhossek,[33] regards the arrangement of chromatic substance in ganglion cells as a purely empirical fact without known significance, and holds that we cannot begin to classify nerve cells until we know how and why structural features stand in causal relation to functional qualities.

A more concrete objection is urged by Benda,[30] who finds that no nucleus is composed exclusively of one type of cell, while impurity in the type is very generally observed.

To these and other similar criticisms Nissl[34] replies that the undoubted existence of transition forms is no essential objection to his scheme of classification; that he does not claim to have settled the whole question of the relation of structure and function, but insists only that the stichochromes of the anterior horn represent typical motor cells.

The strength of this position it is impossible to deny, but it remains for future investigations to determine how far this morphological criterion may be applied to other varieties of cells.

As already stated, in only two types of cells has the minute structure been thoroughly studied by Nissl's and supplemental methods—in the stichochromes of the anterior horn of the spinal cord and the cells of the spinal ganglia.

Structure of the Anterior Horn Cells of the Spinal Cord.

The anterior horn cells are bipolar or multipolar cells, which vary in diameter from 60 μ to 120 μ. Their most striking feature is the arrangement of the chromatic substance in the form of irregular masses, spindles, or large granules, which are found thickly and concentrically grouped about the nucleus, lying parallel to the cell borders, and drawn out into thin rods in the dendrites. Dogiel[35] alone has been able to trace the chromatic bodies into the axis cylinder process, which is generally regarded as being entirely free from chromatic substance, as first noted by Benda[28] in 1885. At the bifurcation of processes is often to be found a distinct triangular mass of chromatic granules called the *bifurcation cone*. Often a crescentic mass is closely applied about a segment of the nuclear membrane, and is called by Nissl the "nuclear cap," a body that is more uniform and distinct in the bipolar cells of the posterior horn of the spinal gray matter. In the spinal stichochromes and spinal ganglionic cells the point of origin of the axis-cylinder process is marked by a crescentic area devoid of chromatic bodies. This area is absent in the ganglionic cells of the retina (Dogiel[36]), in Purkinje cells, and in the cortical pyramidal cells.

The Chromatic Bodies.—It has been generally accepted that the chromatic bodies are composed of a conglomeration of fine granules, although some writers have claimed

that they were occasionally homogeneous. The researches of Held must be admitted to have definitely proven that, treated with the usual fixatives, alcohol, bichloride, etc., they are usually granular, the size of the granules varying with the fixatives employed. (See discussion on technics, page 265.)

Both Held and Nissl agree that in some instances the thinnest sections fail to show any granular structure in the chromatic bodies. In this connection Nissl[37] refers especially to the finely reticulated but not at all granular structures of these bodies in the motor cells of doves and some other animals.

On the question of the state of the chromatic substance in the living cell, opinions have long been at variance. Kronthal,[18] in 1890, examining freshly crushed specimens of spinal gray matter, dried and stained with methylene blue, failed to find any formed chromatic bodies, although the cells were otherwise well stained. Fisher[19] also concluded that the chromatic bodies resulted from the action of fixing fluids, while the living protoplasm of cell is homogeneous.

The studies of Held[9] have furnished important evidence in regard to the condition of the chromatic substance in the living cell. Examining freshly crushed specimens he was unable to find any trace of chromatic bodies in the anterior horn cells of the rabbit. Continued observation showed the appearance of small vacuoles in the cell body and the gradual accumulation about them of fine granules. Cells in this stage fixed in strong alcohol, showed the vacuoles to be located in the centres of chromatic bodies, while the granules proved to be particles of chromatic substance. He therefore concludes that the bodies of Nissl are a precipitate from a previous fluid substance

which is thrown down by fixing agents. The fact that the chromatic bodies become slowly visible when fresh cells are treated with a weak solution of methylene blue he refers to a coagulating or fixing action of the methylene blue.

In a later article he somewhat alters this view, stating that the chromatic bodies appear in the cell within one-half hour after death, without the use of fixing agents, from a process of coagulation occurring as a part of cadaveric changes. In cells examined within three minutes after death he was still unable to find any traces of formed chromatic elements. He finds that 80 per cent alcohol to which has been added $\frac{1}{40}$ to $\frac{1}{4}$ per cent of NaOH fails to precipitate the chromatic substance, which is soluble in alkalies. After treatment with alkalized alcohol the chromatic bodies may still be precipitated by the action of weak acids (after Van Gehuchten's formula, absolute alcohol, 60; chloroform, 30; ac., 10).

The cadaveric precipitation, occurring generally within 12 hours after death, Held refers to the acidity of the central gray matter, which has been shown by Gescheidlen[38] to increase after death.

The writer has repeated Held's experiments with the fresh anterior horn cells of the rabbit, and is convinced that the chromatic bodies are homogeneous in the natural state, that they make their appearance in finely granular form shortly after death and may be demonstrated by weak solutions of methylene blue, either in the moist condition, or in specimens teased after Kronthal's method, or in frozen sections.

Held's studies seem to have proven that the chromatic substance is originally semi-fluid, but it does not appear that this fact interferes essentially with the present views

as to the significance of this constituent of the cell. On the essential point as to the location of the chromatic substance in the living cell, there is no evidence to show that it differs at all from the position in which it is found in stained sections. Moreover, there is no evidence to show that the chromatic substance, whatever its nature may be, is altered in any important respect during fixation, or that it does not pre-exist in some form as a separate constituent of the cell, or that demonstrable variations in its character are not significant of vital processes in cell body.

Dogiel[39] claims that the mere fact that the living protoplasm of the cell is homogeneous is no proof that the chromatic bodies do not exist as such in the natural state, as their refractive power may be the same as that of the cell protoplasm. In his hands a very weak solution of methylene blue in .6 per cent salt solution stains the chromatic bodies well in 5 to 8 minutes, and yet this fluid cannot be said to kill the cell in that time, or at least is not active enough to precipitate the chromatic substance, for cilia, and spermatozoa, and various living larvæ, stain well but remain active for a long time in weak solutions of methylene blue.

There remains to be mentioned in the structure of the chromatic bodies the presence of a ground-substance in which, according to most authorities, the fine granules appear to be embedded, after staining by erythrosin and methylene blue as recommended by Held. This ground-substance appears of a violet color, and where the chromatic granules have been dissolved by alcohol, the ground-substance remains behind unaltered.

Juliusberger[40] demonstrates this substratum of the chromatic bodies by staining thin sections in iodine green

and fuchsine, after which treatment it appears identical in color with the achromatic portion of the cell body.

Van Gehuchten[41] speaks of the chromatic substance as an incrustation on the achromatic reticulum, and identifies the substratum of the chromatic bodies with the achromatic reticulum.

The writer's study of cells which in pathological conditions have lost their chromatic bodies, especially as seen in freshly teased specimens dried and stained on a glass slide, led to the same opinion that Van Gehuchten holds.

An interesting and important inquiry relates to some chemical properties of the chromatic substance. As above noted, Held succeeded in dissolving this substance by weak solutions of NaOH and by concentrated solutions of lithium carbonate, and showed that it is insoluble in weak and concentrated mineral acids, such as nitric, hydrochloric, and by acetic acid.

Eve,[22] on the contrary, found that when sympathetic nerve ganglia were left in weak acids before hardening, the chromatic bodies disappeared, the cell staining diffusely pale blue. There is no apparent explanation of these entirely opposite results. Repeating the experiments of Held, the writer was unable to destroy the chromatic bodies by treatment with several mineral and organic acids, although a raggedness of outline was observed after prolonged (12 hours) exposure to strong solutions. A sat. sol. of lith. carb. also, contrary to the results of Held, did not destroy or alter the chromatic bodies of the medullary cells, although the tissue swelled to twice its natural size in the course of an hour. A weak solution of ammonia, however, completely destroyed all trace of chromatic substance in portions of tissue immersed in this fluid for one hour.

Held found that by treatment with pepsin in a sol. of HCl, at 40° C., the cell body is entirely dissolved, leaving the chromatic masses intact. Millon's reagent he finds to have no effect upon them. Submitted to Lilienfeld's and Monti's microchemical tests for phosphorus the chromatic bodies reacted slightly, and Held concludes that the chromatic substance belongs to the nucleo-albumens. The microchemical reactions of this substance abundantly show that it is not identical with nuclear chromatin.

Benda[30] regards the chromatic granules as related to the basophilic granules of Ehrlich, a supposition combatted by Nissl, Colucci[8] and Heimann,[64] and readily disproven by treatment of sections by Ehrlich's dyes, toward which they do not behave as strictly basophilic bodies, but show characteristic amphophile tendencies.

The Achromatic Portion of the Cell.—Two opposite views are at present actively supported in regard to the structure of the achromatic portion of the cell. The presence of fine fibrils passing diametrically through the cell, with numerous anastomoses, giving often a fine reticular appearance is maintained by Nissl,[42] Becker,[43] Benda,[44] Flemming,[45] Kronthal,[18] Lugaro,[46] Dehler,[47] Dogiel,[36], [39], and many others.

Becker demonstrates these fibrillar structures by Weigert's copper and hematoxylin stain, Kronthal by staining freshly crushed and dried specimens with methylene blue, Flemming by hardening in chromic acid in the chromosmic acetic acid mixture, or with sublimate, and staining with Heidenhain's or Delafield's hematoxylin. Dogiel stains the fresh sections with $\frac{1}{10}$—$\frac{1}{4}$ per cent sol. of methylene blue, having fixed the specimens at various intervals in picrate of ammonia, and demonstrates structures that appear to escape other methods.

On the other hand Lenhossek,[48] Van Gehuchten,[49] Cajal,[50] and Held,[9] are equally confident that the fibrillar structures described by others are not true fibres but rows of fine granules which give the achromatic substance a reticular and spongy appearance.

The latest studies of Held are most convincing of the correctness of this view and that the appearances seen after the cells have been hardened in various fixatives are indistinguishable from those described by Butschli in fluid albumen treated in the same manner. It seems possible, however, that Held, Lenhossek, and Cajal, are not discussing the fibrillar structures that are demonstrated by Dogiel in the retinal cells.

At any rate it is at present impossible to determine which of the two views of the structure of the achromatic part of the cell is correct. The fibrillar theory is most generally accepted, but cannot be said to be the most thoroughly supported. That the achromatic portion of the cell is nevertheless concerned in the function of conducting impulses appears very probable from various theoretical considerations, among which may be mentioned that the continuation of the axis cylinder process is exclusively with this portion of the cell, and that this process is usually composed entirely of achromatic substance, as determined by Simarro[51] and Schaffer.[52]

In addition to the fibrils or granules composing the achromatic substance, other larger granules of somewhat similar staining reactions have been described by Benda,[30] Becker,[43] Levi,[53] and others. It has been claimed by some that these granules represent the metabolic products of the cell (Becker) and that they are increased in number after fatigue of the cell. But little attention has thus far been paid either to the existence or the significance of these elements.

It falls without the scope of this article to more than mention the nearly constant presence of yellowish granular pigment in the adult ganglion cells. This pigment has been shown by Rosin[54] to be related chemically to fat, usually staining black with osmic acid. The presence of this variety of pigment is probably always pathological. A second variety of granular pigment not at all related to the former is found in the cells of the spinal ganglia, sympathetic ganglia, *loc. ceruleus*, *substantia nigra*, etc. The development and distribution of this form of pigment has been studied at some length by several writers, recently by Pilcz,[55] but the relation of the masses and granules to the other elements of the cell still remains unknown.

Nucleus.—The structure of the nucleus of the ganglion cell is rather incompletely shown by Nissl's method. Methylene blue demonstrates a large vesicular nucleus, with a distinct nuclear membrane, a large central nuceolus and occasionally one or more secondary nucleoli (Held), while its further structure is either entirely invisible or is indicated by a fine network of granules stretching from the nucleolus to the nuclear membrane. Some of the various counterstains used in connection with Nissl's method, as the erythrosin of Held, demonstrate the finer structures of the nucleus and their different microchemical reactions.

The ammoniacal carmine solution recommended by Rehm[5] as a counterstain with Nissl's method (carmine, 1; liq. amm. caust., 1; aq. 100, stain 5 min. then decolorize five minutes in alcohol, 100, KNO_3, 1), demonstrates in the centre of the nucleus a rose red mass, which this author seems to regard as a vacuole. With this distinguishing test, he has never been able to find more than

one nucleolus in the normal cell. The writer finds that the central acidophile portion of the nucleolus is brilliantly demonstrated in sublimate preparations by Ehrlich's tricolor fluid, after decolorization in alcohol, nor has he succeeded in finding any such central body in the numerous granules resembling secondary nucleoli to be found in pathological specimens.

According to Levi,[55] all the true chromatin of the nucleus is concentrated in a series of granules lying along the edge of the nucleolus, while the rest of the nuclear network consists of linin.

The writer's study of the structure of ganglion cells has led to conclusions which in one particular, namely, the relation of the chromatic bodies and reticulum to the achromatic or acidophile reticulum are at variance with the views generally accepted. These conclusions are based upon the examination of ganglion cells in normal and pathological conditions, fixed in various fluids, principally Van Gehuchten's, stained in section by methylene blue and by erythrosin and methylene blue, and of freshly teased specimens fixed by heat and stained by the same fluids. In very thin sections of cells prepared as above, by the use of artificial light (32 candle power electric arc), by applying oil to the condenser as well as to the lens (Zeiss apochromatic $\frac{1}{12}$) very clear demonstrations of the cyto-reticulum are obtained. This reticulum is remarkably clear and the relations of the chromatic and achromatic structures appear especially distinct in freshly teased specimens fixed by heat (100° C., 5 min.) Under the above conditions it appears to the writer that the chromatic structures in the cerebral, spinal, and spinal

ganglionic cells are always found in the form of a reticulum with nodal thickenings, which in the stichochromes, reach a considerable volume, covering often several adjoining meshes of the network. The connecting threads of the chromatic reticulum are very delicate in the spinal stichochromes, Plate I, Fig. 1; and spinal ganglionic cells Plate I, Fig. 4; and rather coarse in Purkinje cells, Plate I, Fig. 2.

The presence of this chromatic network is more plainly shown in cells deficient in chromatic substance, in which the fading chromatic bodies may often be seen to resolve themselves into a uniform and delicate chromatic network. (Plate V, Figs. 1 and 2; Plate VI, Fig. 4).

Moreover, a significant pathological lesion, it is believed, consists in partial or complete disintegration, apart from simple fading of nodal thickenings, of this chromatic reticulum. (Plate VI, Fig. 1).

The chromatic bodies and network, as conclusively shown by Held, may appear granular or homogeneous, according to the methods of fixation employed. These conclusions have reference solely to the morphology of the cell in hardened tissues and may have little or no bearing on the relations of the chromatic substance in the living cell.

The results of the present study indicate also that the achromatic or acidophile reticulum depicted by Held is fully demonstrable in specimens stained by methylene blue alone, and is continuous and identical with the chromatic reticulum which the writer has been discussing. Freshly teased specimens fixed by heat and stained by erythrosin and methylene blue are specially convincing of the correctness of this view. In such specimens of the normal human lumbar stichochromes the main dendrite

and adjoining portion of the cell body, an area which may be conveniently termed the "*polar dendrite*" may sometimes be found drawn out into an extremely thin layer, and under these circumstances the relations of the chromatic and achromatic portion of the cell are remarkably distinct. *Here a single reticulum is demonstrable, stainable alike by methylene blue or erythrosin, and when both dyes are used the thinner strands of the reticulum appear bright red while the nodal thickenings are blue.* Moreover, the blue masses fade insensibly into the red and both are everywhere continuous. The meshes of the reticulum are either clear or contain isolated acidophile granules of the same character as the substance ensheathing the dendrites and cell body and continuous with the axis cylinder process.

These indications of the relation between the so-called chromatic and achromatic reticulum accord with the observations made upon sections of hardened tissue stained by the same dyes.

In regard to the strictly achromatic substance of the cell, specimens of the "polar dendrite" prepared as above, show the presence of a granular acidophile substance ensheathing the dendrites, continued in a layer of varying thickness about most of the cell body, visible in many of the meshes of the reticulum, and composing exclusively the axis cylinder process. This substance appears to be identical with the "*axis cylinder geflechte*" of Held, but the accompanying fibrils as well as the serial arrangement of the granules, beautifully shown in Held's drawings, were not visible in the writer's preparations. This view of the structure of the body of the nerve cell appears to be identical in most particulars with that recently formulated by Van Gehuchten.[41]

The appearance in the writer's specimens, however,

fully accord with the observations of Schiefferdecker,[57] Dogiel,[58] Held,[9] and Apathy,[59] that the dendrites contain a granular substance identical with that found in the axis cylinder process, a fact which strongly indicates that all these processes share the function of conducting impulses.

Spinal Ganglion Cells.

The cells of the human spinal ganglia have been exhaustively studied by Lenhossek,[60] Held,[9] Flemming,[61] Nissl,[62] Cox,[63] and Heimann,[64] from whose descriptions the following outlines have been extracted.

These cells are of large size, 60–80 μ in diameter, at times reaching 120 μ. Each cell is surrounded by a connective tissue capsule, often very cellular, and lined by a layer of flat endothelial cells which Lenhossek regards as furnishing nutriment to the contained ganglion cell. The capsule, in the natural condition, is entirely filled by the nerve cell, but in most stained specimens shrinkage of the cell creates an artificial space within the capsule. The cells are unipolar, the process being attached to the body in a knob-like projection, marked off from the rest of the body, as a clear achromatic crescentic area. The chromatic substance usually appears in the form of rather small granules which are distinctly more numerous about the nucleus, but are wanting in a narrow zone adjacent to the nuclear membrane, in a narrow peripheral zone, and at the crescentic area giving origin to the single process. This type of spinal ganglion cells belongs to Nissl's class of gryochromes.

Other less numerous cells contain larger chromatic masses, resembling in structure the spinal stichochromes, while Flemming has described a third class of cells of

moderate size, staining usually rather dark, and containing very coarse granules of chromatic substance. A considerable variation in staining quality may be noted in the cells of the spinal ganglionic cells, a feature referred by Lenhossek to the greater density of the protoplasm, especially of the smaller cells.

Cox describes two main varieties of spinal ganglionic cells. One type contains large or small irregular chromatic bodies without distinct concentric arrangement. The cells of this type may be either large or small. Another type of cell contains large irregular chromatic masses in definite concentric arrangement.

Heimann, in a recent study of the cells of the spinal ganglia in rabbits, especially of their reaction to various dyes, seems to identify the cyto-reticulum with a fibrillar structure. He finds that the chromatic bodies are not continuous with these "fibrils," and he speaks of but one type of cell.

From the study of the cells of the spinal ganglion in the present cases, the writer was unable to find convincing evidence that these ganglia contain more than one distinct variety of cell. (See Plate I, Fig. 4.) While the peculiarities of the chromatic bodies above detailed were noted in many instances, there were indications that these features depended upon physiological or pathological variations rather than upon distinct differences in normal histological structure.

Various grades of pigment deposit, increasing with age, may be found, especially in the larger cells.

The structure of the achromatic portion of the cell may be regarded as similar to that of the spinal stichochromes.

The Sympathetic Ganglion Cell.

The knowledge of the structure of the sympathetic ganglion cell has been contributed largely by Kolliker,[65] Cajal,[66] Retzius,[67] Sala,[68] Dogiel,[69] Vas,[70] and Dehler.[71] These studies refer only in part to the structure of the chromatic portion of the cell.

Vas finds that chromatic substance is absent from the cell in the seven-months fœtus, and that it makes its appearance about the ninth month. At 11–12 years the sympathetic ganglion cell attains its full development, having greatly increased in size and in content of chromatic substance.

Dehler's studies refer to the sympathetic ganglion cells of the frog. These cells measure on the average 10 to 40 μ in diameter and present a great variety of forms determined by pressure of the rather dense connective tissue capsule of the ganglion in which they lie. They are surrounded by an endothelial sheath similar to that of the spinal ganglion cells. The chromatic substance appears in the form of granules or larger spindle-shaped masses, most abundant in the periphery of the cell and arranged concentrically, not about the nucleus, but around a certain point of the cell, or centrosome, which lies midway between the nucleus and the opposite pole of the cell. The large chromatic bodies lie at the periphery of the concentric rings and the finer granules at the centre. The nucleus may be encircled by one or more rows of large chromatic masses. In the centrosome are to be found a group of granular chromatic bodies staining deep black by Heidenhain's hematoxylin.

Dehler follows the technical methods of Flemming, tracing fine fibrils entering the cell from the processes, but does not find that they are connected with the nucleus.

The spiral fibres encircling the bodies of the sympathetic ganglion cells are not demonstrable by Nissl's method. The nuclei of the sympathetic ganglion cells are similar in all respects to those of the spinal ganglion cells. In most of the higher vertebrates, especially in young individuals, double nuclei are frequently seen in these cells. Small chromatophilic cells are rather abundant in sympathetic ganglia.

Dogiel employed the method of vital injection of methylene blue and his investigations were principally devoted to the course and relation of fibres and intracellular fibrils.

According to Dogiel the chromatic masses are usually of moderate size, of oval or angular form, and stain with varying intensity by Dogiel's vital injection method. They are more numerous in central areas, sometimes project beyond the cell borders, are seen in dendrites and even in the crescentic area of origin of the axis cylinder process. By high powers these masses are seen to be composed of fine granules. The intermediate substance is for the most part unstained by methylene blue, but in it are seen a network of fine fibres.

He finds a clear acidophile substance or groundwork about the dendrites and periphery of the cell body, similar to that in the axis cylinder process, and believes that the acidophile substance of the axis cylinder process and dendrites is continuous, running through the deeply stained portion of the cell.

The Structure of Purkinje's Cells.

According to Nissl these cells furnish the type of archystichochromes, their chromatic substance existing partly as large spindle-shaped masses, largest and most

abundant about the periphery of the cell and encircling the nucleus, and partly also in the form of a fine network found throughout the cell body, but most evident near the origin of the dendrites. There seems to be considerable variation in the number and size of the chromatic masses of Purkinje's cells in apparently normal cases. In some of the writer's specimens these bodies appear as densely packed as, though rather smaller than, in the spinal stichochromes. The dendrites of Purkinje's cells contain comparatively few chromatic spindles, but at the bifurcation of processes, even to the third or fourth order, a group of small chromatic granules may sometimes be detected. The presence of several small vacuoles, or as seems more probable, of small highly refractive translucent achromatic bodies, sometimes seen in the spinal stichochromes, is in the writer's specimens, a specially prominent characteristic of the nucleoli of Purkinje's cells.

The writer's sketch of a normal Purkinje's cell was made from a teased specimen dried and stained on a glass slide. The chromatic network and relation of chromatic bodies appear more distinct than in stained sections. (See Plate I, Fig. 2).

Structure of Cerebral Cortical Cells.

The majority of the smaller pyramidal cells of the cerebral cortex belong to the type of pure archyochromes, the chromatic substance being in the form of a fine network of granules, the meshes of which vary considerably in size. This network is traceable for some distance into the larger processes. In some cells the network is distinctly thickened at nodal points, a feature that becomes so pronounced in the deeper layers as to place some of the medium sized pyramidal cells in the class of archystichochromes.

The large ganglionic cells of the motor areas belong to the type of stichochromes, the chromatic bodies being numerous and distinct. The size and number of chromatic spindles in the dendrites is distinctly less in all cortical cells than in the spinal stichochromes.

The Medullary Nuclei.

The *locus ceruleus* and *substantia nigra* are composed largely of medium sized or large stichochromes in which are usually abundant masses of large pigment granules. When the deposit is moderate in amount the outline of the pigmented area may be distinctly marked off from the cytoplasm, in other cases the pigment is very abundant and distributed all through the cytoplasm, being thickly packed between the chromatic bodies.

Throughout the gray matter of the floor of the fourth ventricle and along its walls, the predominating type of cell is unquestionably the stichochrome, but in addition to this type one meets constantly with cells of a different constitution, often apparently belonging to the cranial nerve nuclei. Many of them are, undoubtedly, archystichochromes. Van Gehuchten[31] (p. 237) also depicts such cells in the nucleus of origin the *motor oculi* of the rabbit. The fact that the eighth nucleus contains largely typical stichochromes is hardly in accord with the theory of Nissl's classification, as noted by Van Gehuchten, who suggests that these cells may be cells of origin for the *post. long. fasciculus*, (p. 241, loc. cit.)

The cells of the *olivary bodies* belong to the class of archystichochromes, the chromatic reticulum being rather coarse and nodal thickenings distinct. At an early period, usually before puberty, a considerable area of these cells is converted into an achromatic, highly refractive, slightly

yellowish substance, much resembling the pigmented areas found in many cells and in which the persisting chromatic reticulum is usually very distinct.

The cells of the *external arcuate nucleus* are of the type of archystichochromes, with rather delicate reticulum and large chromatic bodies.

In the *upper medulla* the writer has met with a type of cell which has as yet escaped description, and of which a short reference may here be inserted. These cells are located externally to and above the *locus ceruleus*. They measure 40 to 70 μ in diameter, and are multipolar. They are very rich in chromatic substance, the structure of which constitutes the characteristic feature of the cell. Chromatic bodies are wanting, this substance being found in the form of a network of which the meshes are extremely coarse and thick. The appearance of these cells is totally different from that of any other type seen in the human subject.

At the same level of the medulla single or isolated groups of cells are found, which are identical in structure with those of the spinal ganglia.

An exhaustive study of the normal histology of the cells of the medullary nuclei is a contribution urgently needed, before detailed pathological studies can be conducted with advantage.

During the examination of the central nervous system of a child, seven years of age, dying from shock and hemorrhage, a number of interesting cytological features were observed which are probably characteristic of early life.

The groups of cells in the medulla were much more compact than in the adult. Often four or five cells in

section lay in immediate contact with each other, and some of these cells were distinctly united by broad processes. The chromatic bodies of the large stichochromes were large and extremely abundant. Different types of chromatic structure were more distinct than in the adult, and some groups of cells in the medulla which the writer has never encountered in the adult, presented the structure of the sympathetic ganglion cells.

In new born infants, many of the above peculiarities were noted, but the chromatic bodies at this period were usually very deficient in size and number. The chromatic masses of Purkinje's cells at birth appear to be, as a rule, extremely small and faint.

Babes[72] finds that the "Nissl bodies" are often limited to the perinuclear region, in the normal infant.

Vas[70] has found that the chromatic bodies are wanting in the sympathetic ganglion cells at the seventh month of fœtal life, that they make their appearance in the form of small granules at the ninth month, and are not fully developed until the eleventh year.

Eve[73] also notes the absence of chromatic bodies in the ganglion cells in early fœtal life in the rabbit, finding that only the vagi nuclei in the embryo 2.5 c.m. long contain distinct masses of chromatic substance.

It falls without the scope of the present study to consider further these details of the histology of the medullary and higher ganglionic cells, but it is obvious that until a systematic study of this subject has been contributed, it must remain impossible to accurately interpret the variety of pathological appearances presented by the medullary nerve cells in early life.

Section III.

Physiological Condition of Ganglion Cells in the Central Nervous System.

Considering the great variety of appearances of the chromatic structure of ganglion cells demonstrated by Nissl's method, it is obviously important to know what digressions from the typical and normal aspect of these cells may be expected in the cord and brain of the average normal case.

It is by no means easy to secure at post-mortem material from human subjects in which a fatal lesion has not seriously involved the central nervous system.

The following cases are believed to partially meet these requirements:

Case I.—*Multiple Injuries, Hemorrhage, Shock.*—Male, 14 years; previously healthy. Was struck by a locomotive, receiving internal injuries from which death resulted in three hours, from shock and hemorrage. There was no elevation of temperature, and the patient was conscious until a few moments before death.

Autopsy six hours after death. The body of the first lumbar vertebra, the ramus and body of pubes, were fractured, and the tissues in each locality lacerated and infiltrated with blood. There were a few ounces of bloody fluid in the peritoneal cavity. The viscera were normal.

Microscopical examination. Van Gehuchten's fluid.

The *lumbar cord* was lacerated at the point of fracture and infiltrated with blood for some distance above and could not be used for the present purpose.

In the *cervical cord* the great majority of cells presented an abundance of well-formed compact chromatic masses. The chromatic network connecting these bodies was usually distinct. The nuclei and nucleoli were normal and centrally placed.

In *Clarke's column*, one large cell presented marked central chromatolysis and eccentricity of nucleus. All other cells in several sections were normal.

Immediately external to Clarke's column was a group of medium sized cells, seen in several sections, in which the

perinuclear chromatic masses were moderately subdivided and the nuclei eccentric.

In the *medulla* the majority of cells were perfectly normal in appearance, but it was possible in nearly every section to find some abnormalities.

All the cells of the nuc. XII, appeared normal. Above this nucleus nearly all the larger stichochromes also appeared normal, although the chromatic bodies were very large and of irregular contour. On the other hand, in many of the smaller stichochromes, and in the cells of the other mixed types which are abundant in this region, a moderate subdivision of perinuclear chromatic masses was the rule. A considerable number of examples was seen of central chromatolysis with eccentricity of nucleus.

Throughout the cortex, the appearance of the cells was more uniform. The chromatic bodies were almost invariably compact and regular. Sometimes they were deficient or subdivided in the perinuclear zone. In the archyochromes, attention was drawn to marked variation in the size of the meshes of the chromatic reticulum.

Purkinje's cells were rich in chromatic bodies of rather small size and somewhat indistinct contour.

The results of the examination of this instance were disappointing in the attempt to secure a case showing perfectly normal conditions throughout the central nervous system, and the lesions found must be referred to the severe concussion of the injury, and to the fatal shock and hemorrhage following it.

Barring the slight distortion of the chromatic bodies most evident in the medulla, and the changes in the single group of spinal cells, for which no explanation can be offered, the conditions found indicate a high development and uniform preservation of the chromatic structures in all regions, and to this extent the case serves its original purpose, indicating the physiological condition of the nervous system, in the young normal subject.

Case II.—*Dislocation of Cervical Vertebræ.*—Male, 60 years; fell four stories through an elevator shaft and sustained various injuries. Brought to hospital unconscious, but soon became rational, although there were intervals of mild delirium during the night. There was a fracture of the right femur, and complete hemiplegia below the clavicles. The next morning the patient was entirely rational, and asserted that he felt comfortable. It was noticed that he turned his head to one side, immediately after which he was found dead. Temperature 101.4°.

Autopsy eight hours after death.

There was a reduced dislocation of the third cervical vertebra and the cord at this point was crushed. There was a little fresh blood in the spinal canal and the cervical muscles were infiltrated with blood. The brain and medulla appeared normal. There was a very little extravasated blood in the gray matter of the cord, on either side of the crushed area. The viscera could not be examined.

Microscopical examination. Formalin 10 per cent.

In the *cord*, above the injured segments, the majority of cells showed extensive central chromatolysis, but many of the large stichochromes were intact. In a few cells "axonal degeneration" was noted.

In the *medulla*, the cells of the *XII nuc.* were perfectly normal. In the cells of the superficial *X nuc.*, there was an extensive deposit of yellowish granular pigment, but the remaining chromatic bodies were of normal appearance. The large stichochromes in the region of the *nuc. ambiguus* were intact.

In the *VIII nucleus* nearly all the cells were extensively altered, the chromatic bodies being limited to the periphery, the perinuclear areas being occupied by finely subdivided and partly faded chromatic particles. The nuclei were often eccentric, and pigmentation was excessive.

Apart from excessive pigmentation, and the resulting loss and displacement of chromatic bodies, no changes were noted in the *III, IV, V, VI and VII cranial nuclei.*

In a considerable number of deeper lying cells, in many groups not certainly identified with named nuclei, there was a moderate loss of perinuclear chromatic bodies.

In the *motor cortex*, the giant stichochromes showed extensive pigment deposits, but no changes in the chromatic bodies. In the smaller cells throughout the cortex, the perinuclear areas were often deficient in chromatic substance, and showed an early stage of pigment formation. Elsewhere the chromatic structures were intact. *Purkinje's cells* contained an abundance of chromatic bodies of somewhat smaller size than is usual. A very few of these cells were distinctly deficient in chromatic bodies.

With the exceptions of the extensive pigment deposits, and of the distinct changes in the *nuc. VIII*, which latter the writer is unable to explain, the chromatic structures of the medullary and cortical cells were found in nearly normal condition, and the case appears to furnish a normal standard of comparison for subjects of this age.

Some experimental studies may here be cited on the effects of traumatism and shock on the nerve cells.

After inflicting a severe blow on the abdomen of rabbits, a traumatism proving fatal in from four hours to four days, Parascandolo[74] found by Golgi's method a shrinkage of the cells and rupture of processes; by Marchi's method, degeneration of fibres of Lissauer's column, of the posterior roots, and often of the posterior tracts; by Nissl's method, a considerable variety of forms of chromatolysis. Vacuolation was frequent, but any nuclear changes seen were of uncertain character. He thinks these cellular changes will explain many of the symptoms seen in shock from such injuries.

Luzenberger[75] describes a peculiar concentration of the chromatic substance at one pole of the cortical cell in animals killed by blows on the head. This lesion was limited to the areas most exposed to the traumatism.

The observations of Babes[72] also indicate that in the nervous system of the average adult subject the permanent effects of previous diseases may be found in the presence of a moderate number of altered cells. Clarke's column, the lateral portions of the anterior horns, and some medullary nuclei, he indicates as the regions most often containing such abnormal cells. In aged subjects he rather frequently finds cells that have lost their chromatic bodies, or have become atrophic, as well as those exhibiting extensive deposits of pigment. In young subjects with sound organs, such appearances are much rarer. In animals recovering from various infections he found, after several weeks, many more altered cells in the anterior horns than in control animals.

Section IV.

On Cadaveric Changes in Ganglion Cells.

The writer in sudying the pathological changes in nerve cells in various diseases, was early impressed with the frequency of alteration, which was most naturally referable to post-mortem processes, and being unable to find at that time (1895) any adequate discussion of this branch of the subject, was compelled to make a preliminary study of cadaveric changes in the ganglion cell as demonstrated by Nissl's method. All that has been said in reference to the artifacts produced by fixing agents, is of course of equal import in connection with post-mortem changes. In the writer's experience it has often been impossible to distinguish the one from the other, principally when dealing with vacuolation and the chromatophilic condition.

The course of post-mortem changes in the ganglion cell as revealed by previous methods has been rather imperfectly described by several observers, and among these studies may be mentioned that of Schulz.[76] Recently several studies on post-mortem alterations of the chromatic substance of nerve cells have appeared. Colucci[77] has considered in detail the cadaveric changes demonstrated by Nissl's method. He finds that while adult nervous tissue undergoes post-mortem changes more slowly than most other tissue, yet it does not, even under favorable conditions, enjoy freedom from cadaveric alteration longer than twenty hours. The dependent portions, especially the second and third temporal convolutions and the cerebellum are the first regions to lose consistency. Microscopically, cadaveric changes consist principally in:

First.—Granular disintegration of the cell body, giving it a powdery aspect, or leaving it homogeneous and

diffusely stained. All the elements of the cell are involved in this change, last of all the nucleus, and its prominent characteristic is the uniform involvement of the entire cell body with alterations in the form of the cell. Very early and characteristic changes are to be noticed in the second and fourth layers of cortical cells, while the larger pyramidal cells of the cortex and medulla are more resistant. The fibrillar or achromatic portion of the cell is more apt to show these changes than are the chromatic bodies.

Second.—Colucci notes that various segments of the processes are apt to remain unstained and thus give a false appearance of fragmentation of these processes.

Third.—Complete rupture of processes in various directions may occur in the course of cadaveric alteration.

Fourth.—Black droplets may be demonstrated by Marchi's method, either in the processes or in the cell body, or the entire cell may appear jet black, as the result of post mortem changes.

Neppi[78] noted the course of cadaveric alteration in the spinal stichochromes of the dog. Within six hours after death he found these cells in normal condition. A faint areola about the nucleus was noted, the significance of which appeared uncertain. After 24 hours the chromatic substance appeared normal, but in some cells a slight nuclear chromatophilia was observed. After 48 hours there was a diffuse staining of the entire cell body, but the chromatic bodies appear well differentiated, although often very scarce in the protoplasmic processes. The outlines of the nucleus are less regular, and the karyoplasm shows a light diffuse bluish stain. The nucleus may become eccentric. After 72 hours the changes of the last stage are moderately increased. After 96 hours the cell

outlines are more ragged, the chromatic masses are very scarce in the processes, and in the cell body they stain very faintly. Sometimes the dark areola about the nucleus is much increased in extent. The outlines of the nucleus are irregular and indefinable.

In general, Neppi finds that cadaveric processes lead to a gradual disintegration and fading of the chromatic bodies, accompanied by a shrinkage and chromatophilia of the nucleus. This cadaveric chromatolysis does not, in his opinion, greatly resemble the vital chromatolysis described in various pathological conditions. As the initial alteration he regards of first importance the diffuse staining of the karyoplasm. The irregularity in outline of the nucleus and the shrinkage of the cell body are the most reliable indices of post-mortem as distinguished from vital pathological alterations.

Barbacci and Campacci[79] report a systematic study of cadaveric changes in various parts of the nervous system of rabbits. They used the methods of Nissl, Golgi, and Marchi. Nissl's method revealed, as the initial change, a diminution in the staining capacity of the chromatophilic masses. This change is associated with an irregularity of these bodies, their borders becoming indistinct, and two or more often appearing to be fused together in a larger mass, or the bodies appear to be broken into irregular particles. Occasionally the peripheral masses are entirely bleached, while the perinuclear bodies remain intact. Small areas or the entire cell body are sometimes found homogeneous and deeply chromatophilic.

The granular disintegration of the chromatic masses often gives the cell body a characteristic pulverulent aspect. Vacuoles of various sizes are often seen especially when the protoplasm appears homogeneous. Very

frequently the protoplasm shows a characteristic reticular aspect, the meshes of the reticulum being of varying size and the threads coarsely granular. The irregularity in the size and shape of the meshes of this reticulum serves to distinguish this change from the vital and pathological formation of vacuoles which latter are always rounded and sharply limited. The authors believe that it is quite possible to mistake the initial stages of putrefactive changes for the peripheral chromatolysis so often attributed to pathological processes.

The *nuclei* are sometimes found irregular in outline, sometimes swollen and homogeneous, but with very distinct outlines. The intranuclear network is converted into a series of irregularly placed granules. In advanced stages the nucleus becomes shrunken, ragged, and often homogeneous and deeply stained. In very advanced stages of decomposition the nucleus is indistinguishable, although the nucleolus usually persists in some form. Alterations of the *nucleolus* are relatively late, in cadaveric processes, as observed by these authors. They consist chiefly in eccentricity or extrusion of the nucleolus, in various changes in its form, and, at advanced stages, in swelling and fragmentation. In all these phases there is a progressive loss of staining capacity. In Golgi's method the author describes principally a peculiar irregularity or erosion of protoplasmic processes, which they term the "stato torlato," and which they find to have no resemblance whatever to the varicose atrophy or moniliform condition now generally regarded as of pathological import. The full report of their observations is to appear later.

Levi[80] finds that the first cadaveric changes appear in the cortical cells within 18 to 24 hours after death, in the

spinal ganglia within 36 to 48 hours, and in the cord within 60 hours.

The cells first appear coarsely granular and more intensely stained than usual, while the nuclear membrane becomes indistinct. After this "hyperchromatic stage" the cell body takes on a violet tinge with methylene blue, becomes irregular in outline, while the nucleus loses its identity, the nucleolus only being distinguisable. His studies were upon the central nervous system of rabbits, removed after killing the animals by bleeding, and exposed to the air.

The writer's observations on cadaveric changes in ganglion cells consist in the examination of the brains and cords of rabbits in successive stages of decomposition, and in the study of alterations noted in cases coming to the autopsy table in from one to forty-eight hours after death.

In the course of these observations, the ordinary rules governing the course of post-mortem changes in the cadaver were found to be fully illustrated. In warm, moist weather, advanced decomposition of the central nervous system was found in some cases within six to eight hours, while in the coldest winter weather, the tissues were apparently intact in the great majority of instances after 24 hours. The condition of the tissues before death as determined by the nature of terminal infections proved of very great influence on the rapidity of change immediately after death. Cases of septicæmia, pyæmia, peritonitis, and the infectious diseases, seemed to require that the tissues should be removed and placed in preservative fluids within two to four hours, if one hoped to avoid serious alterations in the finer structure of the cells. In a case of leukæmia terminating in infection by the *bacillus*

aerogenes capsulatus, the most bizarre phases of post-mortem destruction, predominated by gas formation, were found in the brain and cord, although the autopsy was held in January, eight hours after death.

It does not appear possible to state for all conditions any approximate period within which the cellular structure demonstrable by Nissl's stain may be affected by post-mortem alterations.

As a rule, the writer would regard with suspicion any areas showing simply granular disintegration of the chromatic bodies and nuclear chromatophilia, the earliest post-mortem alterations, unless the tissues had been preserved within four to six hours, or in septic cases within two hours after death. In the brains of very young infants the change proceeds with surprising rapidity.

After removal from the body, the brain and cord may be preserved without noticeable change for 26 to 48 hours longer, if kept in cold storage at 32° C. After four days' storage in this way, the brain from a case of eclampsia, showed only a slight increase in the diffuse staining of the nuclei and a slight dimness in outline of the cell body and chromatic masses, which could be referred to cadaveric processes.

A series of observations undertaken for the study of post-mortem changes in the nerve cell consisted in the examination of the central nervous system of rabbits, which had been allowed to decompose in the air for from 48 to 72 hours. Under these conditions the changes seemed to follow a somewhat uniform course. The alterations observed appeared to fall into three distinct periods.

The changes of the *first period* were well marked within 24 hours, and were characterized chiefly by a granular disintegration of the chromatic substance. This alteration

was most uniform and general in the cortical archyochromes which at this time showed an irregular network of larger, more distinct, deeply stained granules, replacing the normal fine granular chromatic network. The achromatic substance at this stage appeared slightly clouded or displaced by vacuoles. The outlines of the cells remained intact. In the spinal stichochromes the outlines of the chromatic bodies were slightly irregular and indistinct and the granules larger. (Bichloride fixation). In the dendrites there was an irregular network of fine granules, and the chromatic spindles appeared more coarsely granular than in the fresh specimens treated by the same methods.

In many instances the nuclei of the cortical cells showed a tendency to stain diffusely but this change was not pronounced.

Characteristic changes early affect the nucleus. The first indication of post-mortem alteration of the nucleus is seen in a progressive clouding of the intranuclear network. This change usually begins about the nucleolus, of which the chromatin appears to diffuse along the intranuclear network producing a diffuse chromatophilia immediately around the nucleolus and extending a variable distance out toward the nuclear membrane. Plate III, Figs. 1–2.

When decomposition is rapid all parts of the nuclear network may be simultaneously affected, and appear uniformly thickened and coarsely granular. Plate III, Fig. 3.

In the *second period*, usually well marked at the end of 48 hours, the characteristic feature was the uniform clouding of the nuclei of the cortical archyochromes. After 24 hours the outer zones of these nuclei were usually clear and retained their delicate intranuclear network. In the second period, the intranuclear network was no longer

visible, and the nuclei almost without exception, appeared evenly and diffusely stained throughout. The nucleolus were sometimes almost invisible. This diffuse nuclear chromatophilia appears to spread from the nucleolus outward, as in many of the larger and less affected cells, nuclei were found showing all transitions from a narrow radiating chromatophilic zone about the nucleolus, characteristic of the first stage, to a dark discoloration of the entire nucleus.

The granular disintegration of the chromatic substance advanced rapidly in this stage, especially in the archyochromes. The normal network was now replaced by an irregular deposit of large discreet granules, often partially grouped, and usually leaving a clear zone about the discolored nucleus. In many cells large and small clear vacuoles appeared, distorting the outlines of the cell body, and disturbing the position of the large granules. In the achromatic substance an increasing chromatophilic tendency was constantly noted.

A characteristic change also belonging in its earlier stages to this period, was observed in the shrinkage of the dendrites which now became irregular in outline and staining qualities, and often followed a wavy or spiral course through the section.

In the spinal stichochromes the nuclear changes were less marked, but the diffuse staining of the achromatic portion of the cell body and dendrites and the irregularity and coarse granulation of the chromatic bodies exceeded those of the first period. In some instances the granular disintegration of the chromatic structures proceeded much more rapidly and at the end of 24 to 36 hours the cell body presented an irregular network of large granules unevenly distributed over the cell

and often found free in the pericellular lymph space. Plate III, Fig. 3.

The *third period* was characterized by the growth of putrefactive bacteria in the finer capillaries and in the pericellular lymph spaces, by the disintegration of the cell body, and by the separation of dendrites.

When bacteria begin to develop in the vicinity, the outlines of the ganglion cells soon become irregular and broken. The perinuclear zone of vacuoles fuses with the large peripheral vacuoles, and these open into the pericellular lymph space often leaving the border of the cell to be indicated only by a single row of dark granules. The process continues until nothing is left of the cell except a dark nucleus with a narrow fringe of dark granules. All stages of shrinkage, rupture, and complete destruction of processes may be followed at this period. The appearance of the nuclei is very characteristic. They are usually diffusely and very darkly stained. The nucleoli usually are much reduced in size but are often surrounded by such a deeply stained area that the central nucleolar spot becomes very indistinct. The nucleoli may also be numerously subdivided.

A striking difference noted in the spinal stichochromes was the resistance offered by the chromatic bodies of these cells to the effects of bacterial invasion. In some instances the cell body was riddled with bacilli and the pericellular lymph space choked with them, while the chromatic masses still retained a distinct outline, undiminished staining capacity, and showed only a moderate increase in the coarseness of their granules. Usually, however, the outlines of the chromatic bodies were irregular and indistinct, and often they were completely broken up into coarse, dark granules. Throughout these periods

the spinal cord proved more resistant to cadaveric decomposition than did the brain or medulla. The fact that Purkinje's cells followed closely the behavior of the other cortical cells rather than that of the anterior horn cells, indicates that the slower progress of change in the spinal cells is referable to local conditions under which these cells are found and not to structural differences. Possibly the smaller content in fluids and the more rapid dessication of the cord may account for some of these differences, yet they were well marked in specimens allowed to remain in the body, where dessication was impossible.

Comparing cadaveric changes found in cases coming to autopsy, under diseased conditions, with the course of post-mortem processes in normal rabbits, much less uniformity was observed.

Extreme differences were noted in the periods required for the development of cadaveric changes in the human subject, so that it is impossible to give any approximate number of hours within which the stages detailed above may be expected to appear. As before mentioned, the rapidity of the process depends upon the ordinary factors governing post-mortem changes, the most important of which seems to be the condition of blood and tissues at death, and next in importance the condition of the surrounding air.

It was often observed that a lack of uniformity existed in the character of the changes, both in different portions of the cerebro-spinal axis and in the nuclei of the same segment of the medulla. Central nuclei were sometimes found more affected by cadaveric processes than were superficial groups of cells.

Yet whatever period the changes might have reached it always seemed possible to distinguish with certainty between post-mortem and vital pathological processes, except when dealing with increased chromatophilia of the nuclei of cortical cells.

The writer has found no evidence indicating that cadaveric changes can simulate the characteristic central chromatolysis so often described as a part of pathological changes. No post-mortem appearances were encountered resembling the conditions seen after insolation. Even in the granular disintegration of chromatic bodies the cadaveric change is distinguishable from the pathological by the large size (bichloride fixation) and density of stain of the resulting granules, and by the uniform involvement of the entire cell.

In the spinal stichochromes of a rabbit dying soon after a subcutaneous injection of the poison of a *water-moccasin*, distortion and granular subdivision of the chromatic bodies was found closely resembling post-mortem disintegration, but distinguishable from it by other features in the cells and surrounding tissues.

In regard to nuclear chromatophilia, the author is inclined to believe that this particular cadaveric alteration is sometimes indistinguishable in itself from a pathological change sometimes observed. Recourse must then be had to evidence obtainable from the probable condition of the tissue and the other characters of the cells.

In this connection may be mentioned some artificial changes probably referable to the traumatism applied during the removal of the brain or cord from the body.

The layer of Purkinje cells may sometimes appear to be separated from the adjoining layer by a zone of tissue

similar to the molecular layer. The writer has found this condition very marked in specimens rather roughly extracted from the cranium and frequently handled, and has been unable to find it when the cerebellum was removed with extreme care and immediately hardened.

It seems probable, that the rupture of dendrites much more frequently results from similar traumatism than from pathological processes.

In some specimens, removed one hour after death, large radially striated or coarsely granular bodies staining densely blue, or sometimes purple, have been found, most abundantly in areas composed of nerve fibres but sometimes occupying the centres of large ganglion cells, distending the cell borders, pushing aside and compressing nuclei and chromatic bodies, or almost entirely obliterating all trace of the cell. These bodies have been described by some as droplets of myelin. They are more abundant in roughly handled tissues.

No evidence was found to indicate that the position of the nucleus is materially altered during the earlier stages of post-mortem decomposition. Later extensive vacuolation may lead to partial eccentricity of the nucleus.

Section V.

Pathological Changes in Chromatic Structures.

Having considered the technics of Nissl's method, the effects of reagents and of mechanical injury on the nerve cell, the normal histology of the ganglion cell in some regions, and the course and character of post-mortem changes, attention may now be turned to the pathological changes in the ganglion cell as demonstrated by this method.

A.—*On Changes in Ganglion Cells in Diseases of Nervous System.*

I.—*Neuritis and Lesions of Nerve Trunks.*—The early observations on pathological changes in ganglion cells revealed by Nissl's stain were largely limited to experimental lesions produced in animals, and it must be admitted that the more definite facts now known regarding the significance of certain changes in the chromatic bodies have been derived from experimental pathology.

Cellular Lesions Following Section of Nerve Trunks.—One line of experimentation rather fully studied has been the effects on the spinal cells of various lesions of their fibres. On this subject many previous investigators have described a variety of changes demonstrated by other methods, principally Marchi's, and leading in the most advanced stages to complete disappearance of the cell. These studies may be found reviewed in the article of Onufrowicz.[81]

Nissl[82] observed that characteristic changes could be induced in the cells of the facial nucleus by tearing out the facial nerve trunk in rabbits. Within 24 hours after this procedure he found that the chromatic bodies of the affected cell, began to disappear in a small area of the cell body. After two days the chromatic masses throughout the entire cell began to break up into a number of fine pale granules. By the third day the same changes affected the chromatic spindles in some of the dendrites, while the achromatic part of the cell began to darken. On the fourth day, he noted progressing disintegration of the chromatic bodies and swelling and irregularity of outline in the cell body. On the sixth day the cell body was rounded and presented a uniformly dusty appearance, while the dendrites were usually invisible. The

nucleus had now migrated to one side, often projecting beyond the cell. By the tenth day, the cells were reduced to irregular waxy-looking or slightly granular masses without nuclei or dendrites. These changes did not affect all the cells of the facial nucleus with equal rapidity, but, on the tenth day, all phases of the above alterations could be seen in different cells.

Without the knowledge of Nissl's work, Onufrowicz followed the changes in the spinal cord resulting from section of the dorsal nerve trunks in cats, considering chiefly later stages of degeneration found six days after the operation. His observations confirm those of Nissl. The anterior horn cells of the affected side and some also of the opposite side were found to be homogeneous, swollen, and entirely devoid of chromatc bodies, or showing only a little granular detritus. Somewhat simular changes with a marked tendency in one case toward chromatophilia were found in the cells of the posterior and lateral horns and in Clarke's column. The nuclei of the cells were often found markedly eccentric and in various stages of degeneration.

Marinesco[83] slightly varied the procedure of Nissl, simply cutting the nerve trunk and observing the changes in the cells of origin. He describes two phases of degeneration in the nerve cell induced by section of the efferent trunk. *First*, there is, according to Marinesco, a loss of chromatic bodies as described by Nissl, beginning about the axis-cylinder process, and effected, as he believes, by a process of hydration. He also noted the eccentricity of the nucleus. *Secondly*, he finds a disintegration of the protoplasm of the cell body indicated by changes in the achromatic substance.

Lugaro[84] studied the effects of transverse section of the

cord in rabbits, and found that all cells within two or three mm. above and below the point of section degenerated, and after a time disappeared. All the cells within four mm. of the point of section, except the anterior horn cells showed the characteristic chromatolysis with swelling and loss of processes as described by Nissl. He concludes, therefore, that the lesions of the cells are greater and earlier the more extensive the lesion of their processes. Lugaro also found that while section of the peripheral roots of the spinal ganglia induces changes which progress to the total destruction of the cell, section of the central roots usually leaves the cells in their normal condition.

Savdovsky[85] ligated the sciatic in rabbits and described the changes in the cells of origin present at the end of four to five days. These consisted in a loss of chromatic bodies at the periphery of the cell and atrophy of many of the angles, concentration of large chromatic masses about the nucleus, and eccentricity of the nucleus.

Flatau[86] also observed all grades of the lesions described by Nissl in the nuclei of origin of the oculo-motor nerve, after section of the nerve in cats.

Charrin and Thomas[87] found in the spinal cord of a guinea pig two months after a double amputation, the changes described by Nissl and others as resulting from section of nerves.

After section of the brachial plexus in rabbits Colenbrander[88] found extensive chromatolysis, eccentricity or loss of nucleus, loss of dendrites, and sometimes extreme swelling of the cell body.

Marinesco[89] verified the observations of Lugaro that section of the central roots of the spinal ganglia induced very slight changes in the cells of the ganglia, while the usual lesions rapidly followed sections of the peripheral root.

Marinesco has also studied the regenerative changes in the cells of the twelfth nucleus 24 days after section of the hypoglossus. At this period he finds that the cells are enlarged, that they stain very deeply from increase in the size of the chromatic bodies, that the nuclei remain eccentric, and that some cells become permanently atrophic. The new formation of chromatic bodies may begin in a central or peripheral ring or irregularly throughout the cell.

Flemming,[90] in an extended study by Nissl's method of the effects of section of nerve trunks on the cells of the spinal ganglia and cord, came to the following conclusions:

(1) The cells of the spinal ganglia are affected earlier (4th to 7th day) than are the anterior horn cells of the cord, but after the fourth week, the changes advance more rapidly in the cord than in the ganglia.

(2) One of the first changes is a shrinkage of the nucleus, often also of the nucleolus, and a lateral migration of the nucleus.

(3) The chromatic bodies first appear to be concentrated about the nucleus where they become reduced in size and number and break up into fine granules. Some remaining chromatic bodies may be increased in size.

The most comprehensive description of the changes in ganglion cells following section of nerve trunks is given in a summary by Van Gehuchten.[91] According to his observations the changes that follow in motor nerve cells affect the chromatic substance only, the underlying network remaining intact, the nucleus showing no degenerative characters, and the cell under favorable circumstances returning to its normal morphology. Such cells cannot be said to reach a condition of true degeneration.

When, however, the peripheral roots of spinal ganglia

are severed or ligated, the cells of these ganglia suffer changes affecting both the chromatic and achromatic substance, and the changes go on to complete degeneration. The reason for this difference in the behavior of motor and spinal ganglionic cells is found in the anatomical relations of the cells. After ligation of the filaments of motor cells the nutrition of these cells is maintained by the trophic influence of adjoining neurons. After ligation of the peripheral filaments of the spinal ganglia these cells, according to Van Gehuchten, are entirely cut off from exciting impulses and completely degenerate. (See also Flatau[86]).

It will be seen that there is not complete accord in the observations of Van Gehuchten and others, and that the facts observed do not fully bear out the very rational theories of Flatau and Van Gehuchten. Onuf and Marinesco describe true degenerative changes in motor cells after section of nerve trunks.

This entire subject requires complete readjustment on the basis of the more minute changes in the chromatic and achromatic structures following ligation of nerve trunks.

The writer's sections of pathological material indicate beyond doubt that long established neuritis affecting motor nerves leads to true degeneration and destruction of the anterior horn cells of the spinal cord. The changes in the achromatic substance and loss of dendrites do not always follow immediately upon the lesion of the fibre, as, in the case of alcoholic neuritis, reported in detail later, the chromatic bodies were largely destroyed in some cells which still retained their cyto-reticulum. In others it was evident that all portions of the cell were affected, the

normal cyto-reticulum was wanting, the achromatic substance was coarsely granular, and the processes were shriveled or absent.

It seems probable that the conclusions now warranted in reference to this subject are that after section of nerve trunks, some cells of origin proceed at once to degenerate and disappear, others merely lose their chromatic substance for a time either to recover or later to pass into a further stage of degeneration. The determining influence in the fate of the cell may very well be the trophic impulses enjoyed by the cell, and the partial preservation of function.

Origin of Changes Following Section of Nerve Trunks.— The results of section of nerve trunks on their cells of origin raises several questions of importance in the physiology and pathology of the ganglion cell. One very natural inquiry relates to the chain of events that leads to these alterations in the anterior horn cells after section of the anterior nerve roots. A more difficult problem is encountered when one endeavors to explain the absence of changes in the spinal ganglia after section of their central roots. Why should section of the peripheral roots of these ganglia induce lesions which are entirely absent after section of the central roots?

Since any direct traumatism to the ganglion cell can hardly be assumed to follow section of nerve trunks, it is necessary to assume that the cellular changes result from a disturbance in the physiological functions of the cell. On this assumption there is not only good reason for accepting the belief in the unity of ganglion cell and peripheral process as embodied in the modern conception of the neuron, but there is also a full explanation of the changes observed in the anterior horn cells after section of

the anterior nerve roots. Such a lesion of the roots by destroying the activity of the cell leads rapidly to changes in the nutrition of the cell which may, in the event of the lesion becoming permanent, progress to complete atrophy. A similar explanation applies to the restoration of the chromatic bodies after the physiological functions of the cell have been restored by union of the divided trunk, as observed by Savdovsky, Marinesco, etc.

In the experiments of Lugaro, after a transverse section of the cord, no changes were found in the ganglion cells below this lesion, except throughout a narrow segment adjacent to the lesion. It would, therefore, appear that the voluntary control of the functions of the anterior horn cells may be inhibited without inducing morphological changes in these cells.

Flatau, in discussing this subject, refers the absence of changes in such conditions to the continuance of the reflex activity of the cell, which of course is not annulled after section of the cord. It then appears that the persistence of reflex activity and presence of peripheral excitation are of greater importance in maintaining the normal nutrition or at least the normal morphology of the cell than is the excitation by voluntary impulses.

It is also possible to suppose that the continued excitation reaching the ganglionic cells through the peripheral roots is sufficient to maintain their nutrition even after section of their central roots, while, on the other hand, section of the peripheral roots leads to atrophy.

A second question of importance is the pathology of the nerve cell here presents itself. Since characteristic changes in the ganglion cells consisting principally in central chromatolysis and eccentricity of nucleus have been found to follow the section of nerve trunks, and the loss

of functional activity in the cell, *is it safe to infer when these characteristic changes are found in ganglion cells that these cells are no longer functionally active?* That such an inference is justified appears very probable from the result of the experiments detailed above. As will be seen later, however, similar lesions of very irregular distribution may be observed in many fatal general diseases, especially of the infectious type, and it is quite possible that other influences not interfering with the conductivity of peripheral nerve fibres may be capable of producing these lesions. A careful study of the conditions under which such typical lesions have been observed by the writer, has furnished no evidence against the view that cells in this condition are no longer functionally active. The further evidence on this point may be derived from the consideration of cellular changes in various other pathological conditions to be described later.

A third important bearing of this series of experimental studies concerns *the relation of cellular changes in the spinal ganglia and gray matter to peripheral neuritis*, especially in alcoholic and diphtheritic cases.

Before the publication of Nissl's method, many writers had described central cellular lesions in peripheral neuritis. (See Ballet[92]). One of the first observations on such lesions demonstrated by Nissl's method was reported by Ballet and Dutil[93] in a case of fatal peripheral neuritis in which the usual appearances of "axonal degeneration" were found in the spinal stichochromes.

Soon after, Marinesco[94] reported a similar case which he had examined some time previously and found central chromatolysis in the spinal stichochromes. In a second case of polyneuritis with lesions in the cord, reported by Marinesco,[95] central chromatolysis was found in the cells

of the postero-external group of cells in the lumbar region, while the achromatic substance remained normal.

The writer's series includes one case of fatal alcoholic neuritis in which advanced and very characteristic lesions were found in the central nervous system.

The patient gave no previous history of disease. Had long been a hard drinker of beer and whiskey. Two months before admission to hospital, he began to have dull pains in both knees, calves, and ankles, followed in a few weeks by difficulty in walking, incapacitating him from work. The paralysis became complete and soon extended to both forearms. There were numbness and tenderness in the extremities but no pain. The knee-jerks were lost. The muscles of the arms reacted to faradism. The muscles of the right leg reacted slightly, those of the left, not at all to faradism. Three days after admission, there was paralysis of the diaphragm, double external strabismus, rigidity of neck and mild delirium. Without any rise in temperature the patient died. Autopsy by Dr. F. C. Wood, to whom the writer is indebted for the material from the case. There were no gross visceral lesions of importance.

Microscopical examination. Alcohol, 95 per cent.

Throughout the *lumbar cord*, the anterior horn cells showed in advanced degree all the changes described as following section of nerve trunks. Nearly every cell showed marked central or complete chromatolysis, with eccentricity of nucleus. Many of these cells had passed beyond this stage, and were entirely lacking in normal characters, containing no traces of chromatic substance and both cell body and nucleus appearing greatly shrunken.

The earlier stages of the same lesions were found in the *cervical cord*.

Throughout the *cranial nerve nuclei* the majority of the cells showed central or complete chromatolysis with eccentricity or protrusion of nuclei. Many of the cells in some nuclei however appeared quite normal. The *nucleus X* and *nucleus ambiguus* were extensively altered.

The cells of the *cortex* and *cerebellum* showed only slight fading of chromatic bodies or appeared quite normal.

The microscopical lesions in the central nervous system

in this case seem to accord in all essential particulars with the clinical history. The affection of the lower limbs was of long standing (2 mos.) and the shrinkage and loss of processes in the cells of the lumbar cord were the evidences of a rather old established lesion. The upper extremities were more recently affected and few of the shrunken cells were seen in the cervical enlargement, although many showed an advanced stage of the usual change.

Respiration and the special senses were affected shortly before death, and in the medulla only the earlier stages of cellular alteration were to be found.

Opposed to these positive results, are the reports of some cases of neuritis in which the microscopical examination failed to show cellular lesions to account for the clinical conditions.

Not much significance can be attached to the report by Courmont,[96] of a case of probable neuritis in a rabbit in which no lesions were found in the cells of the spinal cord. The animal died with paraplegia four days after an intravenous injection of a culture of the cholera bacillus.

Dejerine and Thomas,[97] report a case of alcoholic neuritis with paralysis in which the motor cells of the cord were found to be normal. Three years before death the patient suffered from complete paralysis of all extremities, but had gradually improved until motor power in the arms was normal, while the legs remained paralyzed. Nissl's stain showed no changes in the cells of the cord or medulla. This is an important case, but it appears to stand alone.

Soukharoff[98] also reports a case of undoubted toxic neuritis, in which he was unable to find any changes in the motor cells of the cord.

Carriere,[99] reports an absence of cellular lesions of the cord in two cases of peripheral neuritis, in tuberculous subjects, but the importance of his observations is lessened by the incomplete loss of function in the cases, and by the irregular distribution of the clinical lesions presented.

The negative results reported in at least two of the above cases require that there should be further observations in this department before it can be positively stated with what frequency and extent central cellular lesions may be expected in cases of peripheral neuritis. It seems reasonable to insist that no case should be accepted as showing no central lesions if only isolated groups of muscles are affected, or if every segment of the cord and medulla has not been submitted to the microscopical test.

The weight of evidence seems to be strongly in favor of the belief that every case of established peripheral neuritis is associated with cellular changes in the spinal cord.

Primary vs. Secondary Lesions of the Nerve Cell.—An interesting question developed by the study of central lesions in neuritis relates to the difference between primary and secondary lesions in the nerve cells.

Marinesco[100] was one of the first to note that the central cellular lesions in peripheral neuritis are similar to, though not quite identical with those following section of nerve roots. In one of his communications, he endeavors to distinguish between primary and secondary lesions of this type in the ganglion cell.

When the cell is primarily affected, as after ligature of the aorta, or in Landry's paralysis, Marinesco finds that chromatolysis begins at the periphery of the cell, the nucleus remains central and the achromatic substance

early shows changes such as vacuolation and rupture of processes. In secondary changes, as after section of nerve trunks, there follows partial or complete perinuclear chromatolysis, the nuclei migrate to the periphery, and the dendrites are not broken although their chromatic spindles are reduced in size and number.

The writer cannot find that this plan of distinction between primary and secondary lesions of the nerve cell has been received with much favor. Ballet[92] in discussing Marinesco's and other views and reporting a case of central cellular lesions in beriberi, finds himself unable to state whether the cellular changes of peripheral neuritis are primary or secondary, since the lesions do not follow one type.

Charcot, Marie, Raymond, and Babinski, (quoted by Marinesco) all believe that all polyneuritis depends on a primary lesion of the nerve cell.

Colucci[77] in an exhaustive discussion of pathological changes in ganglion cells demonstrated by various methods, is unable to distinguish between primary and secondary lesions. He finds great similarity between the primary lesions in Landry's paralysis, etc., and those induced by section of nerve trunks. Commenting on Marinesco's views, he concludes that the peculiarities of primary and secondary lesions as described by Marinesco indicate only variations in the resistance of the different elements of the cell, and depend upon the acuteness or chronicity of the morbid process, but do not show distinctly any differences distinguishing a primary and a secondary origin.

The writer's observations on a considerable variety of conditions, support the conclusion of Colucci. The changes described by Marinesco as secondary are certainly

found in the great majority of altered cells in the general toxæmia of the infectious diseases.

That a morphological distinction between primary and secondary lesions should exist seems to be a reasonable expectation, but further studies are needed before it can be demonstrated.

II.—*Myelitis.*—Friedmann's[101] well-known researches on the cellular lesions of acute exudative encephalitis and myelitis were among the first applications of Nissl's method to general pathology, and did much to bring the method into general prominence. After reviewing the scheme of degenerative changes in the ganglion cell, given by Meynert in 1868, Friedmann notes the distinct additions to the knowledge of the subject furnished by Nissl's method.

On the second day of the myelitic process, Friedmann found some cells in an advanced stage of chromatolysis, which he calls "homogeneous swelling." This process, he concluded, begins at the centre of the cell and gradually destroys all chromatic bodies. The dendrites and nuclei are often in good condition when the entire cell body is swollen and homogeneous, but later, the dendritic spindles fade, the nuclear outlines become irregular and indefinite and the nucleolus becomes divided. Another variety of lesion which he regarded as distinct from though often associated with simple chromatolysis, he denominates as "granular (molecular) or fatty degeneration." In this process the chromatic bodies first break up into fine, deeply staining granules, which later lose their affinity for methylene blue, undergo a fatty transformation, and the cell is reduced to a pale granular mass devoid of processes. This alteration is usually seen only in old inflammatory foci, being rare in acute inflammation. Friedmann also noted in some cells a peripheral chromatolysis.

As a result of these studies, and of other previous investigations, Friedmann was convinced that the above forms of change, partially corresponding to Meynert's "simple atrophy" and "cloudy swelling," indicate a distinct pathological condition in the ganglion cell. He was unable to find them in normal specimens or as the result of physiological involution processes (pigment degeneration). He concluded also that a partially degenerated cell may still functionate.

III.—*Landry's Paralysis.*—In Landry's paralysis degenerative changes in the ganglion cell have been described by Ottinger and Marinesco,[102] Ballet,[103] Remlinger,[104] Bailey and Ewing,[105] Marie and Marinesco,[106] Piccinino,[107] and Mills and Spiller.[108] These lesions consisted in all stages of chromatolysis, peripheral, perinuclear, and general; in the molecular disintegration of the achromatic substance, with the formation of vacuoles and clefts; irregularities in cell outline, and rupture of processes (Marinesco); and in a series of nuclear changes, terminating in the loss of this structure. These lesions have been found in cases showing distinct exudative inflammatory changes, both in the vicinity of and at a distance from the inflammatory foci. *In the case of Piccinino, they were of general distribution, but distinct evidences of exudative inflammation were absent, although numerous cocci were found in the vessels and tissues.* This case seems to furnish a much needed transition stage between fatal cases of Landry's paralysis, without lesions demonstrable by older methods, and the well marked forms with myelitis, and would apparently confirm the belief expressed by Bailey and the writer, that the employment of Nissl's stain would serve to explain this enigmatical group of cases, in which no lesions have hitherto been discovered.

IV.—*Tabes.*—It was anticipated that the employment of Nissl's stain in the study of tabes would greatly enlarge the knowledge of the early pathological changes in this disease, if not certainly determine the seat of the primary lesion.

The researches of Wollenberg, Strobe (see Schaffer),[109] and others, who by the application of Weigert's and Van Gieson's staining methods, had demonstrated a considerable variety of lesions in the spinal ganglion cells in tabes, indicated that the primary lesion is located in these ganglia, and that more delicate technical methods might reveal some earlier lesions not previously demonstrated.

Schaffer[110] examined the cord of a fatal case of tabes, with Argyl-Robertson pupil, Westphal's symptom, and joint lesions. The cells of the cervical cord were nearly all normal. In the lumbar region there were some normal cells, but many showed a fine subdivision of chromatic bodies and diffuse staining about the nucleus, while in others, this alteration had become general.

Marinesco,[111] in a case of general paresis and tabes, found marked central chromatolysis and eccentricity of nuclei in the cells of Clark's column. He endeavors to explain thereby the loss of reflexes in this disease, suggesting that the loss of centrifugal trophic influences which no longer reach these cells, on account of the impairment of the sensory root fibres, induces the cellular lesions described. Similar changes, which he states have been found in the anterior horn cells of tabes, may account for the relaxation of muscles and ligaments, characterizing tabes.

On the other hand, Babes and Kremnitzer,[112] as a result of their study of a case of tabes, conclude that the lesions in the spinal ganglia demonstrable by Pal's and a

modified Nissl's method, are inadequate as a basis for the clinical symptoms found in tabes.

Schaffer also found no pathological alterations demonstrable by Nissl's method in the cells of the spinal ganglia in three cases of fully established tabes. The cells showing advanced chromatolysis described by Marinesco in the spinal ganglia of tabes he identifies as the clear type of cells normally present, according to Lenhossek, et al., in these ganglia.

Juliusberger and Meyer[113] also report the entire absence of chromatolytic or other changes in the spinal ganglion cells in two cases of advanced tabes. While agreeing with Schaffer that these cells are usually of normal appearance in tabes, they fail to regard this fact as evidence against the belief that the spinal ganglia are the primary seat of the lesion in this disease. According to Juliusberger and Meyer the normal appearance of the spinal ganglia in tabes may indicate only that these cells have adjusted themselves gradually to their new and abnormal environment and still retaining their functions, at least in part, have preserved their chromatic structures.

Finally, the writer found no marked or characteristic cellular lesions in the lumbar cord of a well advanced case of tabes, dying from intercurrent pneumonia, while the chromatic structures in the cells of the adjacent spinal ganglia were remarkably well preserved. In this case, however, the disease had long been stationary.

The weight of evidence as gathered from the above observations, indicates very strongly that neither is the primary lesion in locomotor ataxia to be found in the cells of the spinal ganglia, notwithstanding the arguments of Juliusberger and Meyer, nor are these ganglia affected in

any degree comparable to the changes found in the posterior tracts of the cord.

V.—*Descending Bulbar Paralysis.*—Marinesco[114] reports, in a case of this description, advanced chromatolysis in the cells of the XII, VII, VI, and III, cranial nuclei and in the anterior horn cells of the lower medulla. He hesitates, however, to claim that these changes are characteristic of the disease, as it is not yet known how often they occur in normal cases, nor what is their relation to the states of activity and repose, nor to what extent they may be produced by fever or artificial agencies.

VI.—*Diseases of the Cortex.*—In *dementia paralytica* Nagy[115] found various phases of chromatolysis and cellular degeneration up to complete disintegration of the ganglion cell. These lesions were most general in the frontal lobes and most advanced in cases with epileptiform seizures. In cases of *mania*, he found the earlier stages of chromatolysis.

Berger[116] examined the anterior horn cells in twelve cases of *dementia paralytica*, and found lesions affecting principally the chromatic substance in 83 per cent of these cases. He failed to find a strict parallel between these cellular lesions and those of the fibres and cortex, or between them and the clinical symptoms of dementia and paralysis.

Boedecker and Juliusberger[117] found a marked reduction in the number of cortical cells and various grades of chromatolysis and cellular atrophy in three cases of *paralytic dementia.*

In *general paresis* Belmondo[118] has described advanced lesions in the cells of the *zona Rolandica* and in the frontal lobe, while in other parts of the cortex the cells were moderately chromatophilic. The type of lesion observed

seems to be that of a molecular degeneration, in which chromatolysis is followed by changes in the achromatic substance, with partial atrophy and marked pigmentation.

Crisafulli[119] also notes in the same disease a great variety of cellular changes, most advanced in the frontal lobes, although the lesions were not limited to this region. He found pallor, granular disintegration and loss of chromatic substance. The cell bodies were often atrophic or contained an excess of yellowish pigment, and their numbers were reduced. The nuclei were often eccentric and all stages of the destruction of the nucleus were observed. While the alterations shown by Nissl's method were not less constant than those demonstrable by other methods, Crisafulli does not consider them characteristic of the disease, or in any way different from those seen in some other diseases.

In *epileptic insanity*, Tirelli[120] describes similar lesions in the cortical cells. He believes that the cellular lesions in the cases are not specific, but depend largely upon nutritive disturbances, probably of the nature of deficient oxygenation. On the other hand, he believes that the lesions of Purkinje's cells are related to distinct cerebral processes, and are specially dependent upon convulsive seizures (Cf. the writer's observations on eclampsia).

In *general insanity*, Christiani,[121] also, describes very distinct cortical lesions. The cells in this case showed peripheral and perinuclear chromatolysis, their outlines were indistinct or irregular. The achromatic substance was chromatophilic and gave evidence of granular and pigment degeneration, and the formation of vacuoles. The processes were often pale, atrophic, and varicose. The nuclei were often granular, deformed, and eccentric.

In a case of *progressive paralysis*, Heilbronner[122] de-

scribed the various milder grades of chromatolysis which he had noted in the cortical cells. The lesions resembled those seen in alcoholic neuritis, and after section of nerve trunks.

In an acute case of *paranoia*, Cramer[123] found the large pyramidal cells of the cortex to be homogeneous, and only in a few cells could he find any granular detritus of the chromatic structures.

In *acute delirium*, Alsheimer[124] describes three distinct conditions of the cortex.

First.—All cortical regions are affected. The cortical cells are distinctly swollen, and there is general chromatolysis; the processes are visible for long distances (partial chromatophilia). The nuclei are little altered. Cases of cerebral neurasthenia (erschöpfungspsychosen) showed changes of this character.

Second.—All cortical regions are affected. The cells are swollen, their processes are traceable for long distances, the chromatic structures are fused together in a spongy or faintly reticulated mass. Nuclear changes are present, there being a distinct tendency toward cellular degeneration. The "intoxication psychoses" are associated with changes of this type.

Third.—The deeper cortical layers are chiefly affected. The cells are in an advanced stage of degeneration and are often atrophic. The nuclei are swollen and irregular. Here belong the cases of acute delirium occurring in the course of chronic mental diseases. From his observations, Alsheimer concludes that the term "acute delirium" at present includes a variety of entirely different pathological processes.

In a case of *idiocy* in a girl two and one-half years of age, Warda[125] found that the cells were reduced in number,

their protoplasm granular, their nuclei pale, and often lacking in nucleoli.

The extensive monograph of Hammarberg[126] translated and published by Henschen, shows that the essential lesions of *idiocy* consist in congenital deficiency in number and development of the cortical cells. The more recent lesions in the chromatic substance of these cells are therefore of secondary origin and importance.

Juliusberger[127] examined the anterior horn cells in two cases of *epilepsy* dying from convulsions, and found all stages of chromatolysis in many cells. He regards these lesions as identical with those seen after ligature of the aorta and in poisoning by arsenic.

The review of the above cases indicates that in various mental diseases, the chromatic structures of the cortical cell are found after death to be considerably disturbed. With the possible exception of the studies of Alsheimer, it does not appear that any connection has been established between these cellular lesions and the mental disorder from which the patient suffered. In most of the reports the authors have failed to detail the immediate cause and manner of death, although, of course, such information is required before any conclusions may be drawn in regard to the significance of the cellular lesions found in these cases.

B.—*Acute Intoxications.*

Much of the experimental study of Nissl's method has referred to the pathological changes in ganglion cells, induced by the administration of various mineral or vegetable poisons.

Arsenical Poisoning.—In 1891 Erlicki and Rybalkin,[128] examining the spinal gray matter stained by carmine, from

cases of chronic arsenical poisoning, noted a loss of striation in the cell bodies which was probably referable to the destruction of chromatic masses. By the same method they observed that the number of cells in the anterior horns was reduced, that the borders of the remaining cells were rounded, that the dendrites were often lost, and that many cells were reduced to a mass of yellowish granules.

Nissl[129] first described the lesion of acute and chronic arsenical poisoning in rabbits. He found as the first effects an increase in size, rounding of contour of the chromatic granules, and deeper staining of the achromatic substance. Soon the enlarged bodies began to grow paler, to look "crumbly," and were at last subdivided into many fine granules, so that the entire cell body appeared "dusty." Finally even the fine granules disappeared, and the cell sometimes went on to disintegration. During the early stage of chromatolysis fine granules appear in the achromatic substance indicating a simultaneous change in this element of the cell. These changes begin at one pole and gradually involve the entire cell.

Schaffer[130] in 1893 also employed Nissl's method in the examination of changes in ganglion cells from arsenical poisoning. He administered 149 cc. of $\frac{1}{10}$ per cent. sol. of potassium arsenite to a dog during 65 days, thereby producing paresis of the hind legs. He found that the first effects of the poison were the appearance of light points in the peripheral chromatic bodies, which gradually increase in size until the whole mass is bleached and pale. In a rabbit dying after six days from arsenical poisoning, the bleaching of the chromatic bodies appeared to affect the entire chromatic mass from the first. Finally, the entire cell body showed a number of small, pale, bluish granules, the detritus of the chromatic bodies.

According to Schaffer, the lesions produced by chronic antimonial poisoning are similar to those from arsenic.

The recent studies of Lugaro[131] of the effects of arsenical and lead poisoning support the results of Nissl and Schaffer. Lugaro finds that the chromatic bodies are at first altered as these authors describe. Later the achromatic substance is involved and when this point is reached the lesion is probably permanent. The character of the lesions produced by mineral and other poisons according to Lugaro, varies both with the nature of the poison and the type of cell.

Dexler[132] has recently reported a study of chronic arsenical poisoning and its effects, in the spinal cells of the horse. He discovered relatively few changes in the cord below the cervical region. In the cervical region many normal cells remained. Others showed a circumscribed area devoid of chromatic bodies, while some were entirely bereft of chromatic substance, or beset with fine granules.

In a few cells the chromatic bodies had become homogeneous and the achromatic substance was deeply stained.

Lead Poisoning.—Schaffer's studies were extended also to the effects of chronic lead poisoning in rabbits and dogs. The first change noted was a subdivision of perinuclear chromatic bodies into fine granules, with the appearance of fine vacuoles in the peripheral bodies, and leading finally to the well known "dusty" appearance of the cell. In many cells he further describes the alterations now termed "diffuse chromatophilia" and regarded as artifacts.

Nissl[133] reports that the changes due to lead poisoning in rabbits consist in granular disintegration of the chromatophilic bodies of spinal ganglionic cells, while only the borders of the larger and more resistant masses are bleached. In the cortical cells, while the chromatic

substance is lost, the achromatic portion stains deeply, and the outlines of the cells are intact.

Sarbo[134] and Nissl[133] both find that in subacute *phosphorus poisoning* the anterior horn cells of the rabbit show chromatolysis, beginning irregularly at one or more poles of the cell, later affecting the entire cell. The nucleus becomes homogeneous and darkly stained.

Somewhat indefinite changes are referred by Nissl to the effects of *silver poisoning*, from which the chromatic bodies of the spinal stichochromes gradually fade, while the achromatic subtance stains deeply and is transformed into a dark reticulated structure. This process leads to a characteristic striation by light and dark lines in the axis cylinder process. Later, the cells become atrophic, but chromatic bodies may persist.

Strychnine Poisoning.—Somewhat peculiar changes have been described by Dehio[135] and Nissl, after poisoning by strychnine. After fatal doses, followed by convulsions, Dehio found that the medial dorsal group of spinal stichochromes was most affected, while the cells of the posterior horns and spinal ganglia remained normal. The chromatic bodies of the spinal stichochromes stained very deeply, and were in some instances reduced to a mass of fine granules.

Nissl finds that in subacute strychnine poisoning, the changes are characteristic. The achromatic substance stains diffusely, while the chromatic bodies are thicker, more closely packed together, and appear coarsely granular. Often these bodies are condensed about the nucleus leaving the periphery of the cell homogeneous, but deeply stained, while the dendrites are very distinct.

Maneresi[136] states that strychnine poisoning causes an

increase in the size of the nucleus, while chloroform reduces the volume of the nucleus in the spinal stichochrome.

Cellular lesions of a very similar character but usually less definite, have been described as resulting from the administration in poisonous doses of veratrine and trional by Nissl[133]; of nicotine by Vas[137] and Pandi[138]; of cocaine, antipyrine, and the bromides by Pandi; of morphine by Sarbo and Saratschow[139]; of bichloride of mercury by Dotto[140] and by Tirelli[141], of carbonic oxide and sulphuretted hydrogen by Borro[142]; and of phosphorus by Rossi[143].

Alcoholism.—The effects of alcoholic poisoning in the ganglionic cells have been investigated by several writers.

Vas[137] first described the alterations induced in the ganglion cells by chronic alcoholic poisoning. After the daily injection of moderate amounts of alcohol, during a a period of 6 to 12 weeks, a state of general malnutrition was produced in dogs and rabbits, and in this condition the spinal stichochromes and spinal and sympathetic ganglion cells, in areas of irregular distribution, showed central chromatolysis or the lesions described by Friedmann as "homogeneous swelling." These changes he regarded as the result of the general malnutrition of the animal and not of a specific action of alcohol.

Dehio[144] described the changes in Purkinje's cells after acute fatal poisoning by alcohol, administered to rabbits through the stomach. In very acute cases no definite alterations were observed. When the animals lived 18 to 36 hours, characteristic changes were noted affecting the whole or a small portion of the body. The chromatic network of Purkinje's cells was replaced by many fine granules irregularly arranged, while the achromatic substance stained diffusely light blue. The dendrites were

usually unaffected and many normal cells were found. No definite lesions were found in other parts of the central nervous system.

Andriezen,[145] investigating the lesions of alcoholic insanity by Golgi's and Nissl's methods combined, found by the latter, in the cortical cells, moderate chromatophilia of the cell body, swelling and indistinctness of the chromatic masses, thickening of the intranuclear network, and increased pigmentation.

Berkeley[146] investigated the lesions of alcoholic poisoning in the cortical nerve cells by Golgi's and Nissl's methods combined. Golgi's method revealed a distinct shrinkage of all cortical cells, varicose atrophy of the dendrites, disappearance of the gemmulæ, and a roughening of the cell body. After Nissl's method, the cell bodies stained more deeply than in normal specimens, the chromatic bodies were indistinct, the achromatic substance was moderately chromatophilic, the nuclei contained numerous fine granules, and the nucleoli were much enlarged.

Stewart[147] verified the results of Dehio, injecting alcohol into the peritoneal cavity of cats. Both in Purkinje's cells, and less evidently in the spinal stichochromes, chromatolysis, most marked peripherally, and diffuse staining of the achromatic portion of the cells, were observed.

The writer is unable to contribute anything in the experimental study of alcoholism, but his series of cases furnish two examples of fatal alcoholism in which very striking cellular lesions were found throughout the central nervous system.

These cases were males, aged 25 and 29 years. They

died after prolonged periods of intoxication lasting six and twelve weeks respectively, in the typical condition of *delirium tremens*. The temperature rose before death to 104° and 105°. One case was complicated by acute degeneration of the kidneys, the other by terminal catarrhal pneumonia of slight extent. These cases represent the ordinary conditions found in fatal alcoholism in the human subject, and in spite of the complications, some of which are almost always present in such cases, are believed to represent in considerable purity, the lesions produced by prolonged alcoholic poisoning in the human subject. No such lesions have been found by the writer after fatal nephritis, pneumonia, or as the result of a temperature of 106°.

The autopsies were made six and twelve hours after death, and the preservation of the tissues (Lang's fluid, twenty-four hours) was satisfactory. In both cases the lesions demonstrable by Nissl's method were nearly identical.

In the *spinal, medullary, and cortical stichochromes* the usual type of lesion was that of extreme chromatolysis. No normal cells were seen anywhere, and in only a few were there any traces of the peripheral ring of chromatic bodies, often seen when the disintegrating process begins about the nucleus.

In many cells, especially in the cranial nuclei, the lesions had advanced far beyond simple chromatolysis, and the cell outlines were irregular and ragged and considerable areas of the cells were almost transparent. The remains of the chromatic bodies appeared as a uniform deposit of fine granules or in the form of a network of fine granules, or no traces of them could be found. In badly altered cells, the nuclei were almost invariably markedly eccentric

or projected beyond the cell border. They were not found to stain diffusely. Yellowish granular pigment was rarely seen in these cells.

Many of the *Purkinje cells* contained a moderate number of large distinct chromatic bodies, but usually these bodies were thin, ragged, granular, or absent, the deficiency being most marked at the poles and not about the nuclei.

In the *cortical archyochromes* the chromatic network was markedly bleached, sometimes coarsely granular and indistinct.

All through the central nervous system, the dilatation of capillaries was striking. In the first case (the patient was said not to have been sober for three months) the chromatolysis was usually more complete than in the second.

It appears, therefore, that acute alcoholism in the human subject is associated with lesions in the ganglion cells, comparable with, but much more marked than those found after experimental alcoholic poisoning in animals, nor can one hesitate to attribute in large measure the violent nervous symptoms observed in these cases, to the cellular lesions revealed by Nissl's stain and only faintly indicated by other technical methods.

Carbolic Acid Poisoning.—Two cases of fatal poisoning by carbolic acid have come into the writer's hands for examination by Nissl's method. The ages of these subjects were twenty-two and forty years. Each had swallowed a large quantity of the acid with suicidal intent, and both died within two or three hours, with the usual well marked symptoms. At the autopsies made twelve and twenty-four hours after death, the gastric mucosa was found deeply necrotic. The brain and cord after removal exhaled a strong odor of carbolic acid, and it was evident that the poisonous agent had reached the

central nervous system in considerable concentration. The cellular lesions found in these cases were indistinct, and unsatisfactory, a result for which the early deaths may be held responsible.

In the *cortical archyochromes* the meshes of the chromatic network were often much widened. The distinctness of the network was unchanged. In the *spinal* and *cortical stichochromes*, the only changes discovered was an irregularity and raggedness of the chromatic bodies. Many of the large stichochromes appeared normal in every respect. About some of these large cells there was a peculiar diffusion of homogeneous chromatic substance, outside the cell, which the writer is forced to regard as artificial, although it was not found in any other conditions. In both cases a few examples of partial perinuclear and peripheral chromatolysis were noted among Purkinje's cells and the cortical and spinal stichochromes.

The examination of these cases failed to show any characteristic lesions as the result of fatal poisoning by an agent inducing pronounced nervous symptoms, such as coma, convulsions, and paralysis, and indicates that the functions of ganglionic cells may be very largely inhibited, perhaps completely, without leaving morphological changes demonstrable by Nissl's method.

That cases of longer duration will furnish distinct general cellular lesions seems very probable.

Hydrochloric Acid Poisoning.—A case of poisoning by hydrochloric acid came under observation during the course of this study.

Male, 48 years. The patient was said by friends to have swallowed the contents of a bottle labeled "muriatic acid." He was seized with violent pain in the epigastrium and brought in an incoherent mental condition to the hospital, dying twelve hours later with symptoms of shock.

Autopsy three and one-half hours after death. There was superficial necrosis of the lips, mouth, œsophagus and stomach. The stomach and small intestine was filled with a bloody fluid of strongly acid reaction. The blood was everywhere fluid and of a brilliant red color. The lungs were very œdematous. The viscera, especially the liver and kidneys, were intensely congested.

Fixation, 97 per cent alcohol. In the *cord* and *medulla* a great variety of the earlier stages of chromatolysis were observed. The main features of the lesion in these cells were the subdivision often minute, of the chromatic bodies, which gave the cells a rather diffusely stained appearance, and irregularity in the outlines of many cells. All cells appeared more or less affected. Central chromatolysis was rare. In the *cortex* the changes were rather more distinct than elsewhere. The large *ganglionic cells of the motor areas* showed extreme subdivision and irregularity of chromatic bodies. The chromatic network of the *archyochromes* was granular and very irregular. No distinct nuclear changes were observed.

Purkinje's cells showed an extreme reduction in the size and number of the chromatic bodies. There was distinct chromatophilia of the achromatic portion of the cell, not affecting the nuclei, which appeared very clear. With the exception of the tendency toward diffuse staining, none of these features can be regarded as specific, while the chromatophilia, if not accidental, is probably to be referred to a slightly altered reaction of the nervous tissue and cannot be regarded as indicating a vital process.

There was one small hemorrhage in the floor of the fourth ventricle at the level of the sixth nucleus.

Morphine Poisoning.—The present series includes three cases of poisoning by morphine.

Case I.—Male, 45 years. Had been addicted to the use of the drug for several years, finally using 16 grains of morphine hypodermically injected, each day, and had suffered in an extreme degree from the general symptoms referable to this habit. Was said to have eaten nothing for one week before death. After a very large injection, quantity unknown, was brought to hospital in coma, dying within a few hours with typical symptoms of morphine poisoning.

Autopsy six hours after death. There was moderate fatty degeneration of heart-muscle, liver, and kidney. The lungs were very œdematous, and the viscera showed

marked venous congestion. The pancreas was very atrophic, being largely replaced by fat. There was considerable œdema of the brain.

Fixation, Lang's fluid, 24 hours.

The chief feature of the changes revealed by Nissl's stain was a marked diminution in the quantity of chromatic substance in nearly all cells of the central nervous system. The chromatic bodies in the cells of the *cord*, *medulla*, *cerebrum*, and *cerebellum*, were very deficient in size and number or often entirely absent. *Purkinje's cells* were very faint, showing a few small, narrow chromatic bodies, very regularly arranged in concentric rings. Nuclear changes, as a rule, were not noted.

In the *medullary nuclei*, there were some cells still retaining chromatic bodies of considerable size but markedly subdivided. In some of these cells the nuclei were shrunken and often eccentric.

The quantity of yellowish granular pigment was much more abundant than usual in most regions of the central nervous system.

Case II.—Female, age 24 years. Had been addicted to the moderate use of the drug for a few months only, but was able to attend regularly to her work as dressmaker. In a fit of despondency she took a large quantity of morphine by mouth, and in spite of treatment, died twelve hours later, with typical symptoms of morphine poisoning.

Autopsy six hours after death.

There was extreme œdema of the lungs, and marked venous congestion of all viscera, but no other gross lesions of importance.

Microscopical examination. Van Gehuchten's fluid.

The *stichochrome cells* throughout the central nervous system showed changes which in many respects were peculiar. When examined with a low power these cells appeared to have lost their normal distinctly striated appearance, many appearing diffusely and unevenly stained, while their outlines were extremely irregular. When examined with a high power, the above peculiarities were found to consist in a marked subdivision of the chromatic bodies, which were enlarged and very irregularly and minutely subdivided.

In the *medulla* the large cells were extensively altered, further, by the appearance of *clefts* in the cell bodies, similar to those described in other conditions by Nageotti and Etlinger.[148] In this region also the loss of chromatic substance was very uneven, some areas of the cells appear-

ing completely bleached, others showing the minute subdivision, while in some spots the chromatic masses seemed fused together.

The majority of the cell nuclei were shrunken and markedly eccentric, while the loss of chromatic substance was as a rule greatest about the nucleus. About many of the nuclei irregular masses and rods of chromatic substance were heaped. See Plate VI, Fig. 5.

Throughout the cortex changes of a similar character were noted. *Purkinje's cells* of the cerebellum were less affected than the cells of most other regions.

The irregularity in the effects of the chromatolytic process, the ragged appearance of the cell borders, the appearance of clefts, and the frequency of central chromatolysis associated with eccentricity of nuclei, are the features peculiar to this case. The last mentioned abnormality is of special interest in connection with the well-known effect of morphine upon the peripheral nerve filaments.

Case III was identical in all important respects with Case II.

Miscellaneous Intoxications.

Effects of Snake Poison—Phisalix, Charrin and Claude[149] report the examination of the nervous system by Nissl's method in a rabbit dying some time after a series of injections with the poison of the viper. Five injections were given in a period of two weeks and the animal fell into a state of cachexia, marked by partial paralysis and anæsthesia of the limbs, and died at the end of three months. The nerve trunks showed advanced lesions of parenchymatous neuritis, while the cord presented the changes of myelitis. A great variety of changes were noted in the cells, including total loss of chromatic structure, loss of processes and beginning atrophic lesions.

Effects of Poisoning by Blood Serum.—Uhlenhuth and Moxter[150] killed rabbits by two to ten daily injections of the serum of beef and human blood, and found uniformly

in the spinal stichochromes the milder grades of peripheral chromatolysis, and swelling of the remaining chromatic bodies. Many of the animals died in convulsions.

Effects of Toxines of Bacillus Botulinus.—In animals dying with characteristic symptoms of poisoning after the injection of the toxines of the *bacillus botulinus* (isolated from decaying meat by Van Ermengen) Marinesco[151] found very extensive lesions of irregular distribution throughout the central nervous system, most marked in the medulla, basal ganglia, and cord. The earlier changes consisted in simple granular chromatolysis, peripheral or perinuclear, with swelling of the cell body and dendrites, and without alteration in the achromatic portion or nucleus. Later, lacunæ formed in the cell body from destruction of the achromatic substance, and it appears from the report that certain nuclear changes were usually but not always associated with this affection of the achromatic structures. The lesions resembled those following experimental anæmia.

Kempner and Pollak[152] report some interesting observations on the condition of the nerve cells in experimental poisoning by the toxins of *bacillus botulinus*. The changes described are very similar to those noted by Marinesco.

In animals dying after a full dose of the toxine there was complete dissoluton of the chromatic structures of the anterior horn cells. The first distinct changes were noted only after the lapse of twenty hours. The injection of anti-toxic serum nine hours after the toxine prevented the cellular changes, and if withheld for twenty-four hours, sufficed to save the animal's life, but not to prevent marked cellular lesions. They failed to find a distinct parallel between the severity of the symptoms and the grade of cellular lesions.

C.—*Auto-Intoxications.*

Eclampsia.—The central nervous system was fully examined in two cases of eclampsia, and the cord alone was secured for study in one other.

Case I—Multipara, aged 38 years, was brought into the Sloane Maternity Hospital in convulsions, which had for fourteen hours been recurring in rapid succession. The uterus was promptly emptied, and the patient kept under light anæsthesia by chloroform. She received also rectal enemata of chloral, an intravenous infusion of hot salt sol. and was placed in a hot pack. The urine boiled solid with albumen, and was finally suppressed. The temperature rose to 106.8°. She died about twenty-four hours after the first convulsion.

The autopsy was held one and one-half hours after death, and revealed advanced chronic diffuse nephritis and hemorrhagic hepatitis, without other lesions of importance.

Microscopical examination. Lang's fluid.

The *spinal* and *medullary stichochromes* showed a great variety of appearances resulting from alteration of the chromatic bodies. A few cells appeared nearly intact. Most of them showed a moderate grade of chromatolysis, usually peripheral. Some had lost nearly all trace of chromatic bodies, and were extremely pale. The nuclei were often eccentric.

In *Purkinje's cells* there was a peculiar type of advanced change, consisting in complete or nearly complete loss of chromatic bodies, with a fine granular network persisting. The nuclei were shrunken and moderately chromatophilic. The nucleoli were enormously swollen, and many contained three to six small vacuoles. Plate VI, Fig. 6.

In the *cortex* the small pyramidal cells were very pale, from deficiency of chromatic network, but without distinct nuclear changes. The large and giant pyramidal cells showed marked subdivision and loss of chromatic bodies.

Case II—Multipara (8th child), 35 years; brought to hospital in semi-conscious condition. There was marked general œdema. The urine was scanty and highly albuminous. There was one violent eclamptic seizure before delivery, which was promptly effected, and one afterwards. A hot pack caused slight diaphoresis, but the pulse failed rapidly, the temperature remaining low, and she died six hours after admission.

The autopsy, twelve hours after death, showed slight chronic nephritis, hemorrhagic hepatitis, a deep cervical laceration, running above os internum. Hemorrhage was partially responsible for the death.

Fixation, Lang's fluid.

Microscopical examination. Lang's fluid.

The *spinal* and *medullary stichochromes*, with few exceptions, showed moderate or advanced chromatolysis, either diffuse, peripheral, or perinuclear. In the *nuc. X* most of the cells showed marked central chromatolysis with eccentricity of nuclei. In the *Purkinje cells* there was minute subdivision of the chromatic bodies, but no nuclear changes. The large and small pyramidal cells of the *cortex* showed moderate grades of chromatolysis of various types.

In a third case of eclampsia, dying on the third day from pneumonia, very slight changes were found in the spinal stichochromes. The brain could not be secured.

With the exception of the nuclear changes in the Purkinje cells of the first case, no peculiar cellular lesions were noted in these cases of eclampsia. The condition of Purkinje's cells being only an isolated observation, it will be sufficient to place it on record without drawing any conclusions as to its probable significance.

Uræmia.—The cellular changes in the central nervous system in experimental uræmia of dogs, have been studied by Acquisto and Pusateri.[153] In the anterior horn cells of the cord they found loss of peripheral chromatic bodies, while the perinuclear bodies had undergone granular disintegration. In the cerebral cortex different stages of chromatolysis were noted. In some cells the peripheral chromatic bodies and the dendritic spindles were normal, while in the perinuclear zones there was advanced chromatolysis. Other cells were homogeneous, and their nuclei dark and indistinct.

Sacerdotti and Ottolenghi[154] also examined the central nervous system in dogs dying four to seven days after ligature of both ureters. By Golgi's method they demon-

strated varicose atrophy of the dendrites while the axis cylinder process remained normal. The lesions were most marked in the cerebral cortex where all cells were affected, but were also abundant in the *pes hippocampus*. Nissl's stain failed to show the chromatolytic changes in the cortical cells described by Acquisto and Pusateri. They did not examine the medulla.

Donetti[155] examined by Golgi's and Nissl's methods the central nervous system of rabbits dying from uræmia after bilateral nephrectomy. By Golgi's method he found varicose atrophy of dendrites with other less definite changes in the cortical, cerebellar, and spinal cells. After Nissl's method there were no distinct alterations in the cortical cells. In the medulla and cord the nuclei of the large cells were very often eccentric, the chromatic substance was reduced in amount, the bodies were finely fragmented, and many cells contained vacuoles. He does not believe that these lesions are characteristic of uræmia.

The writer's series includes six cases of uræmia in which marked cellular lesions were found, of irregular character and distribution.

Case I.—Male, 19 years. Had suffered for one year from frequent headache and nausea. Nov. 9, he suddenly became unconscious, recovering shortly, with paralysis of right arm. Headache and nausea continuing, on Nov. 12, there was a general convulsion, followed by drowsiness. At this time the urine was scanty, s.g. 1010, and contained considerable albumen and a few casts. On Nov. 20 the drowsiness had deepened into coma. Temperature 100°. Nov. 21, after a severe convulsion, he died. Temperature 104°.

Autopsy four hours after death. The kidneys showed extreme changes of chronic diffuse nephritis and were very small. There were no other visceral lesions of importance. The brain and pia were œdematous.

Microscopical examination. Sat. bichloride.

In the *medulla* the cells of the *nuc. XII* were very

slightly altered, the chromatic bodies in a few cells being moderately subdivided. Above the *nuc. XII* there were no perfectly normal cells. The perinuclear zones were usually lacking in chromatic bodies and either entirely homogeneous or presenting a few faint granules. Along the peripheries of the cells, or at the poles, a few bodies usually persisted, but were irregularly clumped or subdivided. Some of the deeper cells were entirely bleached. Many *Purkinje's cells* appeared normal; in most of them the chromatic bodies were finely subdivided.

In the *frontal cortex* the cells showed no distinct alterations, the chromatic network being distinct.

In the *motor areas* the large cells exhibited changes similar to but less marked than those in the upper medulla.

The capillaries were everywhere dilated.

Case II.—Male, 60 years. Excessively alcoholic. Acute illness began April 3, when he was found dazed and helpless on the floor of his bedroom. April 4, he was feverish and complained of pain in the chest and cough. April 6, there were two general convulsions, and he was brought to hospital, comatose, pulse very weak, temperature 104°, urine suppressed. April 8, there were three severe convulsions. Stools involuntary. Urine suppressed. April 9, died; temperature 104°.

Autopsy, five hours after death. The posterior two-thirds of right lower lobe were consolidated. Lying over the spinal column was a single, small, irregular shaped kidney, in a very advanced stage of chronic nephritis.

The pia was very œdematous. The basal arteries were sclerosed.

Microscopical examination. Sat. Bichloride.

The lesions of the nerve cells were similar in nearly all respects to those described in Case I. The changes, however, were more uniform and advanced, and pigmentation was everywhere extreme.

Case III.—Female, 50 years. For three months had suffered continuously from headache, vertigo, œdema of legs, and dyspnœa. The urine contained a large amount of albumen and many granular casts. On her last admission to the hospital vomiting and diarrhœa were added to above symptoms, the urine was often very scanty, and the dyspnœa was extreme. During the last weeks, the intermittent uræmic symptoms became pronounced, and there was continuous mild coma, scanty excretion of urine, and subnormal temperature.

Autopsy one hour after death. The heart was much hypertrophied. The lungs moderately congested. The kidneys were enlarged; the capsules adherent, surface irregular, and presenting a few cysts; the markings greatly distorted.

Microscopical examination. Alcohol 95 per cent.

In the *medulla*, the cells of the *nuc. XII* were very slightly altered, most of them appearing quite normal. Above this nucleus there was uniform subdivision of chromatic bodies in nearly all cells. Central chromatolysis and eccentricity of nuclei were frequent. The superficial *nuc. X*, and nearly all the deeper cells at this level were extensively changed, many of them showing very few traces of chromatic bodies, while the cell bodies were often irregular and the nuclei eccentric. Purkinje's cells showed moderate general subdivision and fading of chromatic bodies.

In the *motor cortex* the chromatic bodies were usually subdivided and often markedly deficient in number. The chromatic network in the cortical archyochromes was usually distinct.

Case IV.—Male, 50 years. Moderately alcoholic. For one year had suffered from cough, spasmodic dyspnœa, anæmia, and dropsy. March 28, admitted to hospital in a state of mild chronic uræmia. On March 30, the delirium had passed into stupor, and urine and stools were voided involuntarily. On April 2, stupor deepened and the temperature, previously normal, rose to 103°. April 3d, with ante-mortem temperature of 107°, he died.

Autopsy, 13 hours after death. Both kidneys were enlarged, and showed advanced changes of chronic nephritis. The pelvis of the right kidney and adjacent renal tissue was the seat of an abscess cavity filled with thick, somewhat dessicated pus. There were many foci of pus throughout the right kidney. The posterior portions of both lungs were partially consolidated. The arteries were moderately atheromatous.

Microscopical examination. Sat. bichloride.

In the *cord* the large cells were usually normal in appearance. In some there was commencing subivision of central chromatic bodies.

The *lower medullary nuclei* were also but slightly altered, most of the cells appearing normal.

In the cells of the *X nuc.* and above this point there was considerable subdivision and loss of chromatic bodies in most of the cells. A few cells appeared normal and some

contained only a few fine granules limited to the periphery or poles.

In the *motor cortex*, the large cells had lost most of their distinct chromatic bodies, but usually a few peripheral masses remained and the chromatic network was distinct.

In *Purkinje's cells* there was considerable diminution in the size and number of chromatic bodies.

Case V.—Female, 63 years. One year previously the right breast bad been removed for carcinoma. For four months she had suffered from cough and dyspnœa; for two weeks, from œdema of legs. The urine had been scanty. March 19, admitted to the hospital, with suppression of urine and vomiting. March 20th, she became drowsy and there were marked muscular twitchings but no spasms. March 21st, deeply comatose. March 22d, died, temperature 99°.

Autopsy six hours after death.

Body much emaciated and very anæmic. There was general carcinomatosis. Both ureters had been lightly compressed by the new growth, causing double hydronephrosis.

Microscopical examination. Sat. bichloride.

In the *cord* and *medulla* many cells appeared quite normal. In the *X cranial nucleus* and above, most of the cells showed a moderate grade of central or diffuse chromatolysis, and in some instances this change was advanced.

In the *Purkinje cells* the chromatic bodies were small and slender, and often deficient in number, especially in the perinuclear zone. There was no distinct powdering of these bodies.

In the *motor cortex* most of the large cells showed advanced subdivision or absence of perinuclear chromatic bodies.

In the archy-stichochromes the meshes of the network were widened and the chromatic bodies finely subdivided. In the *frontal and occipital archyochromes* the meshes of the chromatic network were widened and irregular.

Case VI.—Male, 53 years. Brought to hospital Nov. 10, 1896, delirious, temperature 104°, urine scanty and highly albuminous. Th etemperature gradually fell to 100°, but the delirium, alternating with coma, continued. The urine was finally suppressed. Stools were passed involuntarily. After two days of complete coma the patient died March 24th, temperature 101.°

Autopsy ten hours after death. The posterior portions of both lungs were irregularly and incompletely consolidated. Both kidneys were enlarged and showed the changes of advanced chronic nephritis. In the pelvis of one was a large calculus. The pia was very œdematous, and opaque. The vessels at the base were normal.

Microscopical examination. Lang's fluid.

In the *cord* and *medulla* a few of the large cells appeared normal. Most of them exhibited a moderately advanced stage of central or peripheral chromatolysis, but there were nearly always some remnants of the bodies in all parts of the cell, none being markedly bleached. In the *motor cortex*, the giant cells contained the normal number of chromatic bodies, usually much subdivided in the perinuclear regions.

In the *cortical archy-stichochromes* the chromatic bodies were indistinct and limited to the poles of the cell, the perinuclear zones being partially bleached or occupied by pigment.

In the *Purkinje cells* the changes were of the usual type in uræmia, the chromatic bodies being irregularly deficient in size, form, and number.

General Observations on Cellular Lesions in Uræmia.

The study of the above cases indicates that uræmia, as it occurs in the human subject, is associated with rather marked changes in the chromatic substance of the nerve cells, but these changes are very irregular in character and distribution. As a rule the spinal cells are but little changed in uncomplicated cases. The lesions are most marked in the *medullary nuclei*, especially in the *nuc. X* and above, as well as in the deeper cells throughout the medulla. Here, nearly every variety of chromatolysis may be observed, excepting very advanced or complete bleaching of the cells, which is rare.

The cortical cells are usually better preserved than might be expected from the very marked cerebral symptoms of fatal and prolonged uræmia. In the case dying with severe convulsions (Case II) the cortical as well as the medullary lesions were most marked.

The condition of Purkinje's cells was very uniform in the cases examined, the chromatic bodies of these cells being very irregular in size and shape, and considerably deficient in number.

The effects of pial œdema could not be distinctly traced in the cortical cells.

No distinct or uniform nuclear changes were detected in these cases, although the nuclei were often abnormal in appearance. The achromatic substance of the cortical archyochromes frequently appeared greenish and opaque, suggesting an early stage of pigment degeneration.

In two cases showing a terminal febrile movement reaching 105° and 108°, the cellular lesions did not differ from those seen in cases with subnormal temperatures, and in these cases no changes were found resembling those seen in sunstroke.

The most advanced cellular alterations of the series were seen in the *nuc. X* and deeper cells (nuc. ambiguus) in the case in which severe dyspnœa had been the chief complaint for five days before death.

In general, it seems reasonable to conclude that the lesions of the nerve cells in uræmia are largely referable to local influences and partly also to general toxæmia. Among such local influences may be suggested (1) altered conditions in the peripheral fibres of the cells; (2) local circulatory disturbances; (3) overaction of particular groups of nerve cells; (4) and possibly also the effects of pyrexia.

Finally, in the above cases, there was a fair parallelism between the grade of cellular change and the general severity of the symptoms.

Sunstroke.—The first studies of nerve cell changes in sunstroke as seen by Nissl's method, were reported by Van Gieson (Lambert[156]).

In three cases these authors found throughout the central nervous system, extensive changes in the chromatic structures of the nerve cells. As described by Van Gieson, "The placques in some cells were changed in shape and fewer in number. In others they appeared to be broken into fine dust, and again in others have entirely disappeared. The nucleus stained more deeply than normal, and within the nuclear membrane were some minute spherical granules."

These changes Van Gieson regarded as evidences of an acute parenchymatous degeneration of the neuron, resulting from the action of an autogenous poison which he regards as the basis of the symptoms in sunstroke. (See also Van Gieson[157]).

The present series includes three cases of sunstroke in which the nervous system was examined by Nissl's method.

Case I.—Male, 43 years. Excessively alcoholic, and drinking hard for the few days preceding his seizure. He fell in the street August 7th, 1896, and was brought to the hospital in an unconscious condition. Stools and urine were passed involuntarily. The temperature registered 109°. Treatment by ice pack and stimulation. On the following day he was fairly rational, and highest temperature was 104°. On August 9th he again became delirious and died with temperature of 107°.

Autopsy, fifteen hours after death, showed congestion and œdema of lungs and fatty degeneration of the heart-muscle and liver.

Microscopical examination. Lang's fluid.

In the cervical and lumbar *cord* the large cells stained rather faintly, the chromatic bodies being present, of nearly normal size and shape, but staining faintly. In some cells there was moderate subdivision of chromatic bodies. The nucleoli were nearly all greatly swollen and vacuolated.

In the *medulla*, the same appearances were noted in the larger stichochromes of the cranial nuclei, but in addition the majority of the cells, especially the smaller stichochromes and others, were entirely devoid of chromatic

bodies. The nuclei of these cells contained many chromatic particles, but the nucleoli were not swollen.

In *Purkinje's cells*, very faint outlines of the pale chromatic bodies could with difficulty be distinguished, all of these cells appearing homogeneous by low magnification.

The *cortical cells* were usually quite homogeneous, no traces of chromatic structure being discernible.

In the *posterior spinal ganglia*, the cells were very pale, but here again, the faint outlines of chromatic bodies, often minutely subdivided, could usually be detected. The nucleoli appeared swollen.

In the brain and medulla, less markedly in the cord, all other cells, as well as the ganglia cells, stained very faintly, suggesting that there had been some uniform alteration in the reaction of the tissue which reduced the affinity of all structural elements for methylene blue. No distinct traces of undoubted cadaveric alteration were noted.

The condition of the nerve cells as well as the clinical record, suggest also that alcoholism was quite as important an element in this case as was the thermic fever.

Case II.—Male, 45 years. Found unconscious in the street. Had an empty whiskey flask in his pocket. Brought to hospital comatose, cyanotic, pupils dilated, breathing stertorous, involuntary stools, pulse very feeble, temperature 110°. Died in ice pack fifteen minutes after admission.

Autopsy, eighteen hours after death, showed only fluidity of blood, and intense congestion of viscera. Signs of decomposition were marked in the viscera, but the brain and cord were quite firm.

Microscopical examination. Sat. aq. bichloride.

In the *cord*, the anterior horn cells presented characteristic changes. On low magnification, they failed to show the striated appearance, staining diffusely pale blue. The nucleoli were enormously swollen and pale, and were surrounded by six to ten large deeply staining granules.

With high magnification, it could be seen that some cells still retained traces of chromatic bodies either of the original size and form, or swollen and fused together, or evenly and minutely subdivided, but invariably very pale. These differences may, perhaps, be referred to the varying thickness of the cell body found in the sections. Many cells appeared entirely devoid of chromatic structures. The nuclear membrane was often invisible. The changes

in the majority of these cells were indistinguishable from those found by the writer in over-heated rabbits.

In the *medulla*, nearly all cells showed the more advanced changes noted in the cord. Here many cells were entirely colorless. Some of the *Purkinje cells* were but slightly altered; many contained only a few slender and very pale chromatic masses; some appeared to be devoid of chromatic bodies.

Most of the *cortical cells* failed to show distinct chromatic bodies or network, and the usual nuclear changes were very prominent. In the posterior *spinal ganglia*, most of the cells showed chromatic bodies very pale and minutely subdivided, while many were absolutely colorless. The nucleoli of these cells were much swollen.

In most regions examined, cadaveric changes were noted in the presence of moderate vacuolation and nuclear chromatophilia.

Case III.—Male, 38 years. Alcoholism not certainly known. Treated at another hospital one week before for sunstroke, where he was in a precarious condition, but recovered. On the day of admission fell off a wagon unconscious, and was brought to hospital with usual symptoms. Temperature 109.6°. With treatment in repeated ice packs, he continued twenty-four hours in a half conscious condition, temperature ranging between 97.4° and 105°, but finally died.

Autopsy, three hours after death, showed fluidity of blood, venous congestion of viscera, œdema of lungs, and moderate fatty degeneration of the liver.

Microscopical examination. Sat. bichloride.

In the *cord* the majority of the cells showed a very slight grade of subdivision of the chromatic bodies without any other abnormality. A few cells showed the more advanced changes, with uniform subdivision of chromatophilic bodies, but the loss of chromatic substance was not marked and no very pale cells were seen.

In some of the *medullary nuclei* the pallor and subdivision of the chromatic bodies had reached a considerable degree, and many cells perfectly resembled those seen in Case II, but, on the other hand, the cells in some nuclei showed very little change. In this region, central chromatolysis and eccentricity of nuclei was very frequent in some foci.

In the *cortical cells* the changes in the chromatic structures were not marked, nor in any degree characteristic.

Purkinje's cells, on the other hand, were rather extensively altered, the chromatic bodies being usually finely subdivided, giving the cell a diffusely stained difference.

This case is of special interest as showing that extreme and characteristic lesions in the nerve cells are not always present in sunstroke, and that high temperature alone is inadequate to cause the cellular lesions associated with thermic fever.

The last case was the only one of the three which was comparatively free from the alcoholic element, and the suspicion may well be raised that the marked bleaching of the cells in thermic fever may be partly referable to the complicating alcoholism which is a nearly constant contributing cause in sunstroke.

From extensive studies of the ganglion cells of rabbits, as affected by high temperature, the writer is convinced that the nerve cell changes in sunstroke are specific of this condition, and, in characteristic cases, are distinguishable from most other types of cellular lesions.

Leukemia.

Case I.—Male, colored, 50 years. For past three months had suffered from dyspnœa, general weakness, occasional epistaxis, and pains in the joints. On admission, Dec. 17th, the above symptoms were present, the right knee was swollen and tender, the temperature was 100.° Physical examination negative. Dec. 19th, temperature 103.8°; Jan. 4th there was a mild chill, followed by abdominal pain, tympanites, and temperature 105°. Jan. 8th the blood was examined and 55,000 leucocytes per c.mm., mostly myelocytes, were found. Hemorrhages had occurred from mouth, nose, gums, and bowels. Jan. 9th another chill, temperature 105.4°. Patient in stupor. Jan. 10th, coma, involuntary stools, temperature 104°, death.

Autopsy eight hours after death. The viscera were markedly emphysematous and decomposed, from growth

of *bacillus ærogenes capsulatus*. The abdominal and thoracic lymph nodes were moderately enlarged and very hyperæmic. The spleen was very soft, moderately enlarged, pulp diffluent. The shafts of the long bones as well as all flat bones contained grayish cellular marrow. There were leukemic deposits in the liver, kidneys, and lungs. The brain and cord had escaped marked post-mortem changes and were firm and very anæmic. The pia was œdematous and contained a few small hemorrhages.

Microscopical examination. Lang's fluid.

There was a moderate grade of chromatolysis of very uniform degree throughout the central nervous system. Very few intact cells were found. In the cord, medulla, cerebellum and motor cortex, the chromatic bodies, especially those in the periphery of the cells, were moderately subdivided. The nuclei were usually central and showed no distinct alterations. A prominent feature was the extreme grade of pigment degeneration which affected the nerve cells throughout all parts of the central nervous system.

Case II.—Female, eight years. Had been under observation for four years, suffering from a mixed form of leukemia. During the last few months of the disease, there were extreme anæmia, frequent hemorrhages, extreme enlargement of the spleen. Before death the red cells numbered 880,000, the leucocytes 820,000, consisting of nearly equal numbers of lymphocytes, myelocytes, and polynuclear leucocytes. The patient was confined to bed and quite helpless for three months before death, and during this time there was a moderate febrile movement.

Autopsy six hours after death. The brain could not be secured. The cells of the lumbar cord showed only a moderate grade of central chromatolysis, without special features. The small vessels of the cord were often choked with large mononuclear cells and there were a few larger collections of these cells in the pia.

General Burns.—The present series includes one case of general burns, which proved rapidly fatal.

Female, 40 years. Clothing caught fire from a stove and the skin over three-fourths of the body was severely burned. On admission there was vesication over most of the burned areas, and the patient, though conscious, was in extreme shock. Death ten hours after the accident. The temperature gradually rose, reaching 106.8°.

Autopsy fourteen hours after death. The blood was everywhere fluid, and all the viscera were deeply congested. The brain and cord appeared normal.

Microscopical examination. Ten per cent formalin.

In the lumbar and dorsal *cord* the chromatic bodies were beginning to break up into fine granules and their outlines were very irregular and indistinct. The nuclei appeared normal. The change was most marked about the nucleus. Some cells were apparently unaltered.

In the *spinal ganglia* (lumbar region) there were no cells which retained well-formed chromatic bodies in concentric arrangement. The majority of cells showed only a few scattered chromatic granules and many were entirely bleached. Nuclear changes were absent.

In the *medulla*, the cells were rich in chromatic substance, but the chromatic bodies and network were usually indistinct in outline and partly subdivided. The larger cells of the *nuc. ambiguus* were similar in appearance to those of the cord.

In the higher medullary nuclei, the changes were slightly more advanced, nearly all cells presenting a diminished number of chromatic bodies often partly subdivided.

In the *cortex*, the cells were distinctly paler than normal, from uniform deficiency of chromatic substance. The *giant motor stichochromes* showed marked subdivision and loss of chromatic bodies. Many large pyramidal cells contained no chromatic bodies, but only a faint chromatic network. In *Purkinje's cells*, the size, number, and distinctness of the chromatic bodies were uniformly diminished.

Starvation.—Schaffer[158] described minutely the stages of chromatolysis noted in the anterior horn cells in starving rabbits. Vacuolation was a very marked lesion in these cases, and moderate or extreme nuclear chromatophilia was noted in many cells. Referring these changes directly to malnutrition of the cell, the author concludes that the chromatic substance of the nerve cell represents potential energy.

Tauczek[159] also killed rabbits by complete withdrawal of food and found lesions in the ganglion cells of the cord. After slow starvation he noted disintegration of the chromatic bodies, especially in the spinal stichochromes of the

cervical region. He doubts the propriety however, of referring all changes found under these circumstances to malnutrition of the cells or to any one pathological process.

For the purpose of studying the condition of the nerve cells in states of hunger and complete muscular inactivity, Jacobsohn [160] selected eagles which had been confined in a cold compartment for six weeks, and rabbits killed after being starved for 7 to 10 days. The anterior horn cells of these animals differed in no respect from the normal.

Lugaro and Chiozzi[161] in a study of the cellular changes in the nervous system resulting from prolonged starvation, observed marked degenerative lesions in the cells of the cortex, medulla, cord, and spinal ganglia. These consisted principally in peripheral, central, or circumscribed chromatolysis, vacuolation and disintegration of the achromatic portion of the cell body, and in occasional chromatophilia of nucleus. They used Delafield's hematoxylin to demonstrate the chromatic structures, and noted in the altered cells the distinct reticulated structure of the achromatic substance, where the chromatic bodies had disappeared. The lesions were very irregular in distribution, and not always uniform in degree, while their similarity to the changes observed after poisoning by arsenic or lead was very striking.

The authors conclude that the lesions observed must result from some form of auto-intoxication from intestinal absorption or internal metabolism, which they assume to exist in starving animals.

Donetti[162] has described the lesions in the central nervous system after removal of the suprarenal glands. Guinea pigs survived the operation only 48 hours; rabbits, from 8 to 15 days. The cellular lesions were most marked in the

medulla, but were very irregular in distribution, normal cells lying side by side with extensively altered ones. Some cells seem to be shrunken, others swollen. The nuclei were either central or eccentric. The chromatic masses in the medullary cells were usually reduced to granules and often limited to the poles of the cell. A few cells had lost their nuclei and were in the process of complete degeneration.

Meningitis, Apoplexy and Disturbances of Cerebral Circulation.

Excepting the reference of Marinesco[163] to two cases of pneumonia complicated with meningitis, in which he found the spinal stichochromes but little affected, the writer has found in the literature no reports of studies of the ganglion cells in cases of meningitis.

Dotto and Pusateri,[185] alone, report studies on the cortical nerve cells in cases of intracerebral focal hemorrhages. They found various grades of chromatolysis in the cortical areas whose function had been destroyed by basal hemorrhage. From lesions found in the *Island of Reil* they are led to conclude that this region is connected by fibres running through the external capsule.

The present series includes the following cases of meningitis.

Case I—*Tuberculous Meningitis.*—Male, 29 years of age; suffered from general pains and malaise for one month, headache, nausea, and vomiting, for two weeks, and had been delirious for two days before admission to hospital, Sept. 17, 1896, when he presented distinct symptoms of meningitis, the head being markedly retracted, the limbs rigid and twitching, and the temperature 103°. Delirium alternated with coma, and the temperature remained constant until Sept. 22d, when he died with a temperature of 104°.

Autopsy 13 hours after death.

There was marked œdema of the pia, which was lightly coated with fibrin and pus at the base. The ventricles were considerably distended with turbid fluid. In all these regions and over the cervical cord there were many fine miliary tubercles in the pia. The brain was moderately soft.

There was a small tuberculous focus at the apex of the left lung, and the liver and kidneys showed slight fatty changes.

Microscopical examination. Lang's fluid.

In the *cord* most of the large cells contained the usual number of chromatic bodies, but these were usually very ragged and often finely subdivided.

In the *medulla* the lesions were very irregular in distribution. Most of the superficial nuclei contained cells with many chromatic bodies either well formed or partly disintegrated Similar cells were seen in the deeper zones, but here the majority of cells were markedly bleached, and presented only a few pale bodies along the periphery. A few of these deeper cells appeared entirely bleached.

It was noted that the cells of one nucleus immediately adjacent to a miliary tubercle showed comparatively little change, while the deeper cells lying more remote from the tubercle were extensively altered. Moreover in some foci entirely bleached cells lay next to very slightly altered ones. Plate VI, Figs. 2 and 3.

In the *motor cortex* the giant cells usually showed marked central chromatolysis, a few were entirely lacking in chromatic bodies, while a few others appeared very little affected. In the *arkyochromes* the network was usually paler than normal. *Purkinje's cells* contained an abundance of chromatic bodies, which were usually reduced in size, irregular in shape and often partly subdivided.

Case II.—*Tuberculous Meningitis.*—Male, 30 years of age. Formerly alcoholic. Illness began January 1, 1897, with symptoms of pulmonary tuberculosis of subacute character. Admitted February 22d, with signs of severe general bronchitis, without pneumonia or cavities, temperature 104°. Urine, 5 per cent of albumen.

On February 23d, he was mildly delirious and passed considerable blood from rectum. Maximum temperature, 103°. On the 27th there was vomiting, diarrhœa, great restlessness, mild delirium, temperature uniform. These symptoms continued until March 1st, when he became comatose, and on March 2d, died, temperature 108°.

Autopsy eight hours after death. The pia over the convexity was dry and granular, at the base œdematous. The ventricles were slightly distended with turbid fluid. The brain was distinctly softened. There were everywhere many fine miliary tubercles. The cervical cord was involved.

The lungs showed the lesions of subacute miliary tuberculosis of moderate extent.

Microscopical examination. Sat. bichloride.

The description of the previous case applies accurately to the present one, with some minor differences. In the second case the tuberculous process was much more active, following the vessels for some distance into the tissues. The marked bleaching of many large cortical and medullary cells described in the first case was seldom seen in the second. It may be noted that coma and rigidity were distinct and prolonged and the distension of the ventricles greater in the first case. In the second, the temperature was much higher and the general toxæmia more intense, but the cellular lesions were less advanced.

Case III.—*Sporadic Meningitis.*—Female, 18 years. Illness began June 28th, 1896, with vomiting and convulsions, passing into coma, which continued till death. On July 1st, the day of admission, there were several convulsions; maximum temperature, 104°. July 4th, several convulsions; temperature, 104.5°. July 6th, the coma deepened; temperature, 102°. July 7th, the breathing became rapid and stertorous; temperature, 105°. July 8th, there was complete coma and the patient died with ante-mortem temperature 105°.

Autopsy seven hours after death. The entire pia and brain were much congested. The pia was everywhere opaque and over the base and along the sulci moderately thickened. The ventricles were not distended nor markedly inflamed. There were no visceral lesions of importance.

Microscopical examination. Lang's fluid.

The pia over the base, convexity, and cervical cord, was much thickened and infiltrated with leucocytes and large mononuclear cells. There were numerous small extravasations of blood. Along the vessels of the brain and medulla there was moderate infiltration with round cells.

The condition of the ganglion cells was similar in most details to that found in the first case of tuberculous meningitis.

CASE IV.—*Chronic Hemorrhagic Pachymeningitis.*—Female, 78 years. Had suffered for six months from headache, gradually increasing hemiparesis with muscular contractures, and from tremor resembling that of paralysis agitans. Two days before death she became unconscious, and died without marked rise of temperature. (The writer is indebted to Doctor Frederick Peterson for the reference to this case).

Autopsy four hours after death. The dura all over the convexity was markedly thickened, lamellated, and infiltrated with blood. In the meshes of pia and arachnoid there was a little free blood widely distributed in a very thin layer over a large area of the convexity. The pia was considerably thickened. The arteries at the base were slightly atheromatous. The cord and viscera could not be secured.

Microscopical examination. Ten per cent formalin.

The preservation and staining were excellent, but thin sections were needed to avoid the appearance of chromatophilia.

The *superficial nuclei of the medulla* were almost entirely normal in appearance, except for excessive pigmentation of the cells.

In the deeper lying cells there was usually an early stage of uniform chromatolysis, the perinuclear bodies being rather finely subdivided.

In the *cortex*, there was also in many cells a slight grade of chromatolysis, but the majority of cells were practically normal. Beneath the thickest portion of the blood clot, the lesions were more general and advanced than elsewhere.

In *Purkinje's cells* there was a moderate reduction in the size and number of the chromatic bodies.

The absence of advanced lesions in this case may reasonably be referred to the lack of serious disturbances in the cerebral circulation. There was very little extravascular blood in the pia, and the resulting increase of intra-cranial pressure must have been comparatively slight.

CASE V.—*Chronic Hemorrhagic Pachymeningitis.*—Male, 37 years. Brought to hospital by ambulance, having had five convulsions. The convulsions continued and he died a few minutes after admission, temperature 101.8°.

Autopsy six hours after death. There was considerable blood in the meshes of a thickened dura over both

sides of the convexity. There was a flat blood clot 10 x 7 cm. and 1 cm. in thickness, lying in the meshes of arachnoid, compressing right parietal lobe. The pia was everywhere moderately thickened. The blood vessels at the base of the brain were normal. The left ventricle was moderately hypertrophied. The lungs showed evidences of chronic congestion. The kidneys were moderately enlarged, capsules not adherent, surface smooth, markings irregular.

Microscopical examination. Lang's fluid.

In the *medulla* the lesions were neither extreme in degree nor very uniform in distribution. Most of the large stichochromes in the lower medulla contained many pale but not disintegrated chromatic bodies. There were, however, isolated examples of advanced chromatolysis. Higher in the medulla and in the deeper lying groups, some moderately bleached cells were observed.

In the *cortex beneath the clot*, the chromatic bodies were limited to the periphery and those present seemed reduced in size. The perinuclear zones were moderately bleached. Many of the large cells, however, showed only a beginning subdivision of perinuclear masses.

Beyond the limits of the clot most of the cells appeared intact.

In *Purkinje's cells* the chromatic bodies were pale, near the dendrites deficient, but elsewhere present in nearly normal number and appearance.

The absence of advanced changes in this case may be referred to the rapidly fatal effects of the hemorrhage. Although no definite history of the beginning of the attack could be obtained, it seemed certain that death followed the initial seizure within two or three hours.

Case VI. — *Chronic Hemorrhagic Pachymeningitis.* — Male, 50 years. For three months had suffered from severe headache and was unable to work. December 1, 1896, he was unable to walk, and was thereafter confined to bed. About January 1st, 1897, he became partially comatose, opening his eyes when roused, but soon relapsing into unconsciousness. January 2d, coma deepened and continued without other noteworthy symptoms, until death, January 12th. The temperature during this period was between 99° and 101°.

Autopsy eight hours after death. The posterior portions of both lungs were partly consolidated from catarrhal pneumonia. The entire convexity of the

brain was evenly compressed by a layer of clotted blood and fibrin derived from a thickened and lamellated dura-mater. This blood clot was 1 to 1.5 cm. in thickness and must have exerted considerable pressure upon the underlying brain tissue.

Microscopical examination. Lang's fluid.

The *cortical cells* from various regions showed a marked deficiency in chromatic substance. In the *motor regions beneath a thick mass of blood*, very few cells showed any distinct traces of chromatic bodies, the majority of cells being extremely bleached, but still retaining a distinct chromatic network. In some cells a few traces of the chromatic bodies persisted in the form of a peripheral ring of small granules. Beyond the limits of the blood clot, these changes were less marked. In the *cerebellum*, which was free from clot, Purkinje's cells contained a considerable number of chromatic bodies moderately reduced in size, and often limited to the perinuclear zone, or the base of the cell.

Case VII.—*Subacute Leptomeningitis.*—Male, 7 years. Had tonsilitis in June, 1896. A few weeks later had a chill, followed by fever, lasting a few days, and had a mild general convulsion. Slight cough and irregular pains continued until September 16th, when he passed a restless night, waking with fever, repeated vomiting, great thirst, and within a few hours had five general convulsions. On admission, the patient was in stupor, temperature 104.8°. September 17th, stupor and delirium, temperature 106°. Urine and stools passed involuntarily. September 18th died, temperature 107.5°.

Autopsy three hours after death. The lungs were congested. The consistence of the liver was reduced and outlines of lobules indistinct. The spleen was moderately enlarged. There was extreme engorgement of all cerebral sinuses and pial vessels. Over the frontal lobes there was a slight effusion of bloody serum along the course of the pial vessels. The ependyma was dry. The pia was congested and opaque, the cortical gray matter darker than normal. No tubercles nor foci of blood or pus were present.

Microscopical examination.

In the *cord and medulla* the large cells showed all stages of destruction of chromatic bodies, many cells in the medulla especially, being entirely bleached. In these bleached cells the underlying reticulum was sometimes

visible, often indistinguishable. Irregularity in outline of cell body, and eccentricity of nucleus were frequently seen. No normal cells could be found.

In the *motor cortex*, the large cells showed all stages of chromatolysis, and many were entirely bleached. The small cells exhibited a pale chromatic network with a few small chromatic granules at one or more poles.

Purkinje's cells were usually extremely bleached, but many still showed faint remnants of chromophilic bodies.

There was everywhere extreme congestion of the blood vessels and marked dilatation of pericellular lymph spaces.

The pia was greatly thickened by a new growth of connective tissue, infiltrated with blood, round cells and leucocytes. A few cocci in short chains were seen in sections.

Case VIII.—*Subacute Traumatic Meningitis and Encephalitis.*—Male, 28 years. January 7th, 1898, was struck on right temporal region by a falling iron door. Was rendered temporarily unconscious, and afterward suffered severe and continuous headache, located in this region. He was often drowsy, but not delirious, and had no spasms or paresis. On admission, February 1st, temperature was 100.2°; pulse, 90; right pupil slightly larger than left; internal strabismus of left eye; some stiffness of neck; spastic rigidity of legs and arms; increased reflexes; no anæsthesia or hyperæsthesia. February 2d, restless, moving hands constantly in incoordinate manner. Temperature 103°. February 3d, mildly delirious, involuntary urine, temperature, 103°. February 4th, stupor, temperature 103.8°. February 5th, internal strabismus more marked. Legs rigid; delirious; temperature 104°. February 6th, temperature 105. February 7th, died, temperature 105°.

Autopsy four hours after death. Over two-thirds of the left convexity, dura, pia, and brain are tightly adherent, and about this area the pia is granular, extremely congested, and ecchymotic. The underlying brain substance is much congested. In left superior occipital fossa, dura and pia are adherent to skull. Both ventricles are moderately dilated with turbid fluid. There are no fractures. Viscera congested.

Miscroscopical examination. Alcohol 95 per cent.

In the *motor cortex* beneath the adherent membranes the chromatic bodies of the giant cells are invariably very

irregular in shape, often much faded and usually much subdivided. In some cells the entire perinuclear zone is replaced by fine granules, and in thick sections appears opaque. The nuclei stain diffusely. In the archystichochromes the chromatic bodies are usually limited to the poles and are subdivided. The chromatic network is everywhere retained. On the opposite side of the brain the meningitis is slight, and the same lesions rather less marked are to be observed.

On the under surface of the cerebellum there is a layer of exudate of considerable thickness. Here the *Purkinje cells* are very deficient in chromatic bodies, which when present, are faint, irregular, and subdivided. Many cells show no bodies, but only a distinct but irregular chromatic network.

On the floor of the fourth ventricle in the region of the locus ceruleus and III, IV nuc. there is a rupture of tissue, extending a few lines beneath the surface, and covered with fresh exudate.

The cells of this region are similar to those of the motor cortex, showing marked subdivision of chromatic bodies, while the chromatic network and granular remains of the chromatic bodies are distinctly visible.

In the *lower medulla* the changes are much less marked, many normal cells appearing.

Case IX.—*Intra-ventricular Hemorrhage.*—Male, 30 years. Without previous illness was suddenly seized on March 28th with pain in the head, and was admitted to hospital with right hemiplegia. The paralysis was incomplete and the muscles rigid. Temperature 100°. Urine, passed involuntarily, was highly albuminous. There was deep coma. March 30th, coma persisted, temperature 103°. March 31st, coma and paralysis complete, temperature 107°. Died.

Autopsy four hours after death.

The pia was moderately œdematous, and, over posterior surface of cerebellum, infiltrated with bloody serum. The ventricles were considerably distended with clotted blood and serum. The left optic thalamus, Island of Reil, internal capsule, and temporo-sphenoidal lobe were the seat of a large hemorrhage, 7 to 8 cm. in diameter. The arteries at the base were atheromatous, and there was advanced chronic nephritis.

Microscopical examination. Sat. bichloride.

In the *medulla* the cells of the superficial nuclei show

general and, in the large cells, usually complete chromatolysis. In the cells which are not bleached, there is usually a single mass of chromatic substance at one side or pole.

In the *frontal and motor cortex* chromatolysis is extreme, most of the large cells presenting a wide homogeneous area about the nucleus, in which the cyto-reticulum is with difficulty distinguished.

Some *Purkinje cells* contain the normal number of chromatic bodies, but these are usually very small and slender. Many are entirely bleached. In some the bodies are limited to a narrow peripheral ring.

Case X.—*Extra-dural Hemorrhage.*—Male, 24 years. Fell from a wagon on the evening of March 31st, was rendered unconscious, had one convulsion. Brought to hospital 2 A. M. April 1st, in coma, pupils widely dilated, not reacting to light, breathing slow, stertorous, complete paralysis of limbs. Temperature 105.2°, pulse 64. Died at 4.50 P. M., temperature 109°.

Autopsy ten hours after death.

The entire coronal suture was separated ¼ cm., the fissure crossing the groove of the left middle meningeal artery and passing into left medulla cerebral fossa. The left middle meningeal artery was ruptured. The dura was separated from the skull over an area 14 cm. in diameter by a large firm blood clot. The underlying convolutions were flattened, but not lacerated. The under surface of the left temporo-sphenoidal lobe was extensively lacerated.

Microscopical examination. Sat. bichloride.

The viscera were uniformly congested.

Throughout the *medulla* the deeper cells are extremely deficient in chromatic substance, many being entirely bleached, and the others retaining a very few small irregular masses at one or more poles. The superficial nuclei are slightly less affected.

Throughout the *motor cortex*, more marked on the side of the blood clot, all cells are extensively bleached, the remains of chromatic bodies being scanty, minute and usually limited to the periphery of the cell. In the arkyochromes the network stains faintly. In *Purkinje's cells* the chromatic bodies are uniformly deficient in size, usually also in number, but the lesions are much less advanced than in the motor cortex.

CASE XI.—*Thrombosis of Basilar Artery.*—Male, 35 years. Admitted to hospital for operation on incarcerated inguinal hernia, but on day of admission became comatose and operation was postponed. The coma rapidly deepened and without convulsions or marked elevation of temperature, he died, about 36 hours after the onset of cerebral symptoms.

Autopsy twelve hours after death. There was an incarcerated and partly strangulated right inguinal hernia. The lungs contained a few areas of catarrhal pneumonia. In the kidneys there were a few old infarcted areas. There was moderate general arterio-sclerosis.

At the middle point of the basilar artery there was a firm thrombus entirely occluding the lumen. The brain was moderately œdematous, but there were no areas of softening.

Microscopical examination. Lang's fluid.

Throughout the *medulla* all the large cells are either completely or almost completely lacking in chromatic bodies. In some cells the remains of the chromatic bodies are visible as fine, pale granules scattered irregularly throughout the cell body. In most cells the cyto-reticulum is retained, and there are no evidences of nuclear changes.

In the *cortex* nearly all the large pyramidal cells are very deficient in chromatic substance, but many of them show a few small masses at one or more poles. In the smaller cells the chromatic network is visible but faintly stained.

In *Purkinje's cells* there is a striking diminution in the size and often in the number of chromatic bodies. Many of the cells contain a few pale and very slender rods.

The chief features of this case are the extreme bleaching of the medullary cells and the uniformity in the cellular lesions in this and other regions.

The study of the foregoing cases indicates that purulent and tuberculous meningitis are usually associated with lesions in the chromatic structures of the ganglion cells often of extreme grade, but not of uniform distribution. Immediate proximity to a purulent or tuberculous meningitic process does not necessarily destroy the chromatic

bodies in these cells. On comparison of these cases of meningitis with those of hemorrhagic pachymeningitis in which are added the elements of pressure from extravasated blood or anæmia from thrombosis of vessels, *it will be seen that the character of the lesions changes and that the extreme grades of chromatolysis are, as a rule, uniformly present in the compressed or anæmic areas. Moreover, this fact is the more striking because the effects of bacterial toxine are absent in these latter cases.*

The lesions found in the cases of thrombosis of basilar artery and various forms of cerebral hemorrhage, were equalled in intensity only in cases of alcoholism, sunstroke, tetanus, etc., but not in cases of severe general bacterial toxæmia. The conclusion seems justified therefore that the chromatic substance of nerve cells is more susceptible to the effects of disordered circulation than to the action of most bacterial toxines.

In many of the cases attended with high temperature the lesions were more advanced than in those in which the fever was moderate, but no uniform effect could be traced to this cause.

The severity of the lesions seemed to depend almost entirely upon the extent and duration of the pressure or anæmia (Cf. Cases V and VI).

The relation of cellular changes in the cranial nuclei to the neuritis of cranial nerves commonly present in meningitis, could not be thoroughly studied at this time, but is an interesting subject deserving investigation. "Axonal degeneration" was a common medullary lesion in the cases of meningitis.

In connection with the cases of cerebral hemorrhage it is important to refer to Neumeyer's study[186] of the effects of mechanical pressure upon the cortical cells. Neumeyer

inserted lead plates beneath the skulls of rabbits, diminishing the intracranial capacity about $\frac{1}{20}$. After a few hours of such pressure, the superficial cells showed a progressive loss of chromatic substance both in the nucleus and cytoplasm, the chromatic bodies often being massed into clumps and appearing coarsely granular.

After ten days, only a few granules of chromatic substance remained in the cell body, usually in the perinuclear zone. Often the nuclear membrane seemed to have disappeared. Many cells had lost all trace of cytoplasm, only the shrunken nuclei remaining. These lesions extended about 10 mm. beyond the limits of pressure, gradually fading into normal tissues.

Of similar interest also are the experiments of Pellizzi[187] which indicate that the simple loss of function of the cells in these cases is not sufficient to account for the destruction of the chromatic bodies of the cells. Pellizzi separated the frontal lobe in dogs from most of its fibrillar connections, while leaving the blood vessels partly intact, and found thereafter very minor changes in the chromatic structures of the nerve cells, which remained practically normal for many days. Some of the animals lived as long as two months.

D.—*Infectious Diseases.*

Typhoid Fever.—The writer has been unable to find any complete reports of the examination of the central nervous system by Nissl's method in cases of typhoid fever.

Marinesco,[163] however, states that in two cases of typhoid fever he found very slight cellular changes associated with marked vascular disturbances, such as hyperæmia and hemorrhage.

In typhoid fever and diphtheria Babes[72] refers to the

cellular lesions in the cord as consisting in chromatolysis, vacuolation, and loss of nucleus and nucleolus, associated with vascular changes and increase of round cells.

The present series includes two cases of typhoid fever.

CASE I.—Male, 36 years. Had been confined to bed with fever and diarrhœa, and had been delirious four days before coming under observation. On admission, Oct. 22, 1896, the patient was actively delirious, temperature 105, with distinct signs of severe typhoid infection.

Oct. 23, maximum temperature 105.5°. Urine and stools passed involuntarily, pulse very rapid and feeble. Death Oct. 23; terminal temperature 103°.

Autopsy three hours after death. Nearly all the Peyer's patches were the seat of deep necrosis. There were many small ulcers throughout the colon.

The spleen was very large and soft. The mesenteric lymph nodes greatly swollen. No other visceral complications.

Microscopical examination. Lang's fluid, 24 hours.

In the *cord* nearly all the stichochromes showed moderate subdivision of chromatic bodies, most marked about the nucleus. In the *medulla*, the ganglion cells showed all the less advanced types of chromatolysis. In some cells, especially of the *nuc. X* and deeper areas, only a few fine chromatic granules were left. The periphery of the cell was sometimes more affected than the perinuclear area, and in many instances there was a diffuse powdering of all bodies, most advanced near the nucleus. The cells of the *nuc. XII* were little changed, those of the *nuc. X* and *nuc. VIII* and deeper cells above, more markedly.

In the *olives*, the cells showed only a narrow peripheral ring of subdivided bodies.

In the *locus ceruleus* many cells looked normal, others were very deficient in chromatic bodies. The pigment was here of normal appearance.

In the *Purkinje cells* there was uniform diminution in size and often also in numbers of the chromatic bodies, whose arrangement was still regularly concentric.

CASE II.—Male, 35 years. Said to be excessively alcoholic. Illness began Dec. 16, 1896, with fever, prostration and diarrhœa. On admission Dec. 20, the patient was mildly delirious, temperature 104, abdomen moderately distended, slight œdema of legs. The delirium and fever

continued unchanged until the 26th, when he became partially comatose, with temperature 105°. On the 28th, the urine and stools were passed involuntarily. With persistent high temperatures, delirium and stupor, on January 2, he died, with slight indications of perforation, and with a terminal temperature of 105°.

Autopsy five hours later. There was a localized purulent peritonitis in right iliac fossa about a perforated ulcer. The lungs contained numerous small areas of catarrhal pneumonia. There were many large and nearly healed ulcers in the location of Peyer's patches, and some more recent ones in the upper colon.

Microscopical examination. Sat. aqueous bichloride. 12 hours; bichloride and formalin 5 per cent; and bichloride and sat. aq. picric acid (aa).

The cord was not examined.

In the *medulla* there was a very marked loss of chromatic bodies, affecting the perinuclear zone or the entire cell body or leaving a few subdivided or irregularly fused chromatic masses at the poles of the cell. The lesion is distinct in the *XII*, *X* and *VIII nuclei*. The deeper cells, including the *nuc. ambiguus* and *nuc. lateralis* showed more pronounced changes, many cells being extremely bleached, often with eccentric nuclei, irregularity of outline, and loss of cyto-reticulum.

In the *cortex* the giant motor stichochromes showed changes similar to those of the medulla. The arkyochromes showed irregularities and partial bleaching of the chromatic network, retaining clumps of chromatic substance at the poles only, and are often ragged in outline. There is distinct pulverization of chromatic bodies in the larger dendrites.

Purkinje's cells were extensively altered, exhibiting many of the more advanced types of chromatolysis. Some of these cells were entirely bleached.

The results of the examination of two cases indicate that in typhoid fever there are cellular lesions of considerable intensity and of general distribution throughout the central nervous system. It would seem that these lesions increase with the duration and severity of the general toxæmia, and are partly influenced by a prolonged high temperature.

They appear also to be essentially connected with the

profound nervous disturbances which accompany fatal typhoid infection.

In the above cases the lesions were much more pronounced than in cases of pneumonia of equal duration.

Pneumonia.—Dejerine[164] in 1897 reported a case of pneumonia, duration three days, with low delirium and a maximum temperature 43.3° C, in which he had examined the spinal stichochromes by Nissl's method. These cells were much altered throughout the cord, being swollen, homogeneous, and presenting only traces of chromatic bodies. The nucleoli stained poorly. Dejerine did not believe that this chromatolysis was accompanied by any marked symptoms, nor could it be considered as a lesion of importance.

Marinesco[163] reports similar results from the examination of two cases of pneumonia complicated with meningitis, and also in broncho-pneumonia.

In the cases complicated with meningitis the anterior horn cells were found unaltered. In cases of broncho-pneumonia, various grades of chromatolysis were noted in the spinal stichochromes. Marinesco seems to refer the result in the latter instance to "the immediate action upon the cells of the more virulent toxine of broncho-pneumonia, while in the first cases the toxines appear to have exhausted themselves in producing the vascular lesions of meningitis."

Marinesco goes on to infer, on grounds not stated, that the lesions of nerve cells in infectious diseases depend upon the age of the individual, being more marked in old persons, upon the intensity of the virus, on the duration of the disease, and as Goldscheider and Flatau[165] have shown, upon the fever.

The present series includes four cases of pneumonia in

which the central nervous system was examined by Nissl's method.

Case I.—Female, 48 years. Two weeks before admission began to suffer from cough with mucoid and blood-stained sputum. Ten days later had a severe chill, complained of pain in the side and was prostrated. On admission was comatose, with paralysis of left limbs, dilated pupils, temperature 106.5°. All symptoms persisted and she died on the 17th day. Temperature 105.5°.

Autopsy 24 hours after death. The upper two-thirds of right upper lobe were consolidated. The pia all over the base and convexity and for some distance down the cord was œdematous and lightly coated with pus, containing large numbers of capsulated diplococci. There was slight chronic nephritis.

Microscopical examination. Lang's fluid, 24 hours.

There was everywhere evidence of post-mortem change consisting in moderate nuclear chromatophilia and vacuolation of the bodies of the ganglion cells.

In the *cervical cord*, which was lightly covered with pus, most of the chromatic bodies were moderately subdivided and irregular, some were but little changed, and a few cells appeared normal.

In the *medullary nuclei* the changes were of the same type but more distinct. The *XII nucleus* was but slightly affected. The *X nucleus* and deeper lying cells were extensively changed.

In the *cortex*, there was a moderate subdivision of chromatic bodies in most of the larger pyramidal cells, but the chromatic network was usually well preserved. Many of the *Purkinje's cells* were extremely deficient in the size and numbers of the chromatic bodies, some appearing almost completely bleached but showing a distinct underlying network. Others were but little changed. Pigmentation was everywhere excessive.

Case II.—Male, 28 years. Brought to hospital delirious, temperature 103°, with consolidation of both lower lobes. Alcoholism suspected. Alternating delirium and stupor continuing for three days, the temperature remained uniformly high, reaching 109° before death, on the fourth day of observation. The urine was moderately reduced in quantity, slightly albuminous and contained coarsely granular casts. All lobes were partly and the posterior portions entirely consolidated. The liver was

slightly fatty. There were signs of moderate chronic nephritis. The pia was very œdematous. The case was a typical example of acute lobar pneumonia in an alcoholic subject.

Microscopical examination. Lang's fluid, 12 hours.

No normal cells were anywhere seen. In the *spinal*, *medullary* and *cortical stichochromes* the usual type of lesion was that of extreme chromatolysis. In only a few cells was the peripheral ring of subdivided chromatic bodies still present. In the *medulla* many cells were entirely bleached, largely infiltrated with pigment and showing extreme eccentricity of nuclei. In many of these cells the underlying reticulum could not be distinguished. *Purkinje's cells* were much less affected than the medullary nuclei. Throughout the medulla there was well marked circumvascular infiltration with round cells of both the pial and deeper vessels. The lesions in this case are probably referable more to alcoholism or high temperature than to the pneumonia.

Case III.—Male, 55 years. Moderately alcoholic. Illness began with severe chills, cough and rusty sputum, and continued for two weeks with the usual symptoms of pneumonia. On admission, at the end of the two weeks, there were signs of consolidation of right upper and lower lobes. The temperature ran between 100° and 102°, till just before death when it rose to 105° F. The patient was emaciated, vomited occasionally, and appeared stupid. The urine was slightly albuminous. Death on the eighteenth day.

Autopsy twelve hours after death. There was consolidation of most of right lung, but no signs of alcoholism or nephritis. The pia was very œdematous.

Microscopical examination. Sat. bichloride, 24 hours.

In the *cord* and *medulla* there was very marked subdivision and loss of chromatic bodies in all the larger cells. The nuclei were often eccentric. Some cells retained small but distinct chromatic bodies. Pigmentation was moderate. Some of the cells closely resembled those seen in the case of alcoholic pneumonia, but none were found entirely bleached.

The *cortical stichochromes* and *Purkinje's cells* showed only moderate subdivision of chromatic bodies.

Case IV.—Female, 40 years. Was seized on July 4th with chills, headache, vomiting and pain in chest, followed

later by cough with bloody expectoration. On admission the temperature was 104° F.; there were signs of consolidation of the right upper lobe and the patient was delirious. The delirium or coma continued, the temperature rose to 106° and remained at that point for five days when with marked abdominal distension and violent delirium the patient died.

Autopsy two hours after death. There was consolidation, with the production of new intraalveolar connective tissue, of the right upper lobe. The pial and dural veins were gorged with blood. The pia was œdematous and, over the cerebellum, infiltrated with blood-stained fluid. The ventricles and brain substances appeared normal.

Microscopical examination. Sat. bichloride, 8 hours.

In the *XII cranial nucleus* there was very slight subdivision of chromatic bodies.

In the *X cranial nucleus*, *nucleus ambiguus*, and all the deeper cells in this region of the medulla there was extreme chromatolysis, with irregularity of cell outlines and frequent eccentricity of nuclei. The same conditions, rather less marked, were noted in all the other cranial nuclei. The nuclei in the cells of the *locus ceruleus* were invariably eccentric, often bulging. In most of the *Purkinje cells* the chromatic bodies were moderately subdivided. In the *motor cortex* there were some typical examples of central chromatolysis, but many of the giant stichochromes were entirely intact.

From the above cases it appears that uncomplicated acute lobar pneumonia may run a fatal course even with exaggerated nervous systems, without leaving uniform changes in the ganglion cells demonstrable by Nissl's method. In all the cases examined, the upper medullary nuclei were extensively altered, having lost most of their chromatic bodies, but the *nuc. XII* and the cells of the cord were not markedly changed or were practically normal, in uncomplicated cases.

In one case there was prolonged violent delirium while the cortical cells showed very slight lesions, irregularly distributed, and the majority of large cells appeared normal.

The ordinary temperature of fatal pneumonia (106°) appears not necessarily to leave any changes in the ganglion cells such as are seen in cases of sunstroke or in rabbits subjected to high temperature.

In the case of alcoholic pneumonia with terminal temperature of 109° the extreme bleaching of the cells recalls the very similar lesion in cases of sunstroke, but these changes are indistinguishable from those resulting from acute alcoholism and in this instance were possibly referable to the alcoholic element.

There seems to be no good reason to deny that there is an essential connection between the failure of the heart and respiration in fatal pneumonia and the changes in the ganglion cells of the medullary nuclei, and it seems probable also that the exaggerated activity of the cells is the determining factor in the production of lesions.

Diphtheria.—Pernici and Scagliosi [166] report the examination of the central nervous system in cases of diphtheria. In the *cortex* they found many normal cells, but some were much faded, very pale, and a portion of their protoplasm was entirely uncolored, while the nuclei were small, and the dendrites appeared granular. By Golgi's method such cells showed varicose atrophy. The changes in the cord were indefinite. Many of the cells appeared smaller than normal and their protoplasm was granular. The nuclei were often shrunken. A few cells had lost their processes and were reduced to a mass of coarse granules.

In guinea pigs killed or dying 5 to 22 days after subcutaneous injections of diphtheria cultures, Murawjeff [167] found in the anterior horn cells all grades of chromatolysis, reaching complete bleaching, and followed by degeneration, loss of nuclei, and vacuolation. The lesions were more marked in the lumbar than in the cervical cord.

The spinal ganglia were unaffected in four or five days. Many fibres in peripheral nerve trunks were degenerated.

In a later communication Murawjeff[168] reports that diphtheria anti-toxine causes very similar lesions in the nerve cells as does the toxine. When, however, the toxine and anti-toxine in neutralizing doses are injected simultaneously the nerve cells remain unaffected.

Acute Bronchitis, Asphyxia.—Male, 45 years. Had suffered repeatedly from attacks of bronchitis with spasmodic asthma. Brought to hospital March 10, 1897, breathing rapidly, very cyanotic, temperature 102°, with signs of severe general bronchitis. March 11, labored breathing and cyanosis continued without improvement, temperature 102.5°. March 12, all symptoms aggravated. March 13, died with extreme cyanosis, temperature 103.5°.

Autopsy 11 hours after death.

The blood was dark and fluid. The pleura and pericardium contained numerous ecchymoses. The lungs were intensely congested; the bronchi were thickly coated with muco-pus. The cerebral sinuses and pia were gorged with blood.

Microscopical examination.

In the *medulla*, the cells of the *nuc. XII* were usually normal in appearance. In the *nucleus X* and deeper lying cells the chromatic bodies were usually limited to a narrow peripheral ring, the remainder of the cell showing a more or less distinct chromatic network often infiltrated with yellowish pigment.

The same changes were very marked in the cells of the *corpora quadrigemina*. In the cortex the large cells showed a loss of chromatic bodies in a perinuclear or peripheral zone of variable extent. The chromatic network of the *arkyochromes* was regular and distinct.

In the *Purkinje cells* the chromatic bodies were usually of large size and regular contour, but deficient in number at the bases of the dendrites.

Septicæmia.—In this group are included five cases of general sepsis, including peritonitis, empyema, pyæmia, cellulitis.

Case I.—*Peritonitis.*—Male, 49 years. Had been excessively alcoholic. For four months before admission had

suffered from epigastric pain and marked tenderness, frequent vomiting of blood and occasional tarry stools, and had become excessively anæmic. Four days before death, he had sharp pain in the epigastrium, was prostrated, and died with symptoms of general peritonitis. The temperature remained about 101°. The last examination of the blood showed 10 per cent of hæmoglobin.

Autopsy 8 hours post-mortem. There was a circular ulcer of the duodenum which had perforated at one point directly into the peritoneal cavity. The peritoneum was everywhere the seat of a purulent inflammation and contained about one pint of free pus. There were evidences of chronic gastritis, fatty degeneration of the heart-muscle and liver, acute exudative nephritis, and extreme anæmia.

Microscopical examination. Lang's fluid.

In the *cord* many of the large stichochromes appeared normal or showed only a little raggedness of the chromatic bodies, probably of cadaveric origin. Others exhibited distinct signs of chromatolysis, either central or peripheral. In a few cells the chromatic bodies were all minutely subdivided.

The above description applies also to the cells *throughout the medulla*, although here the changes were slightly more general and distinct.

In the *cortex* most of the cells were very nearly normal, showing, with few exceptions, only slight subdivision of a few chromatic bodies, or slight irregularity of network. In the *Purkinje cells* the chromatic bodies were usually abundant, clear, and of normal size, but in a considerable number there was beginning subdivision of peripheral chromatic masses.

In nearly all regions there were frequent evidences of post-mortem change consisting in nuclear chromatophilia, diffuse staining, and vacuolation.

Case II.—*Empyema.*—Female, 22 years. Was delivered of a first child on February 24, 1897, after a dry labor of fourteen hours' duration, by forceps and craniotomy. Had been unwell for several days before admission when she had a temperature of 103.8°, and there was a fetid discharge from the vagina. After delivery she developed signs of pneumonia. The temperature ranged between 102° to 103° F. for twelve days; on March 11, following a chill, it rose to 105°, and just before death registered 107.2°. During the last eight days, there was mild delirium, with subsultus, nystagmus, unequal pupils, and on

March 11 the patient was in deep stupor. There was a purulent vaginal discharge from the first, continuing, with the uterus well involuted, until death, March 12.

Autopsy 8 hours post-mortem. There were two litres of thick fetid pus in the left chest, and an abscess cavity 4 cm. in diameter in the right broad ligament and uterine wall. The liver was very fatty. There was a moderate chronic nephritis. There were no signs of meningitis.

Microscopical examination. Sat. bichloride.

In the *cervical cord*, most of the larger cells appeared nearly normal, but some showed a slight raggedness or subdivision of the chromatic bodies. In the smaller cells the changes were more marked and the central areas of the cells were often bleached or diffusely stained.

In the *medulla* there were very general lesions. Some cells showed distinct "axonal degeneration." In others the fragmentation of chromatic bodies was uniform. Some of the larger cells appeared normal. In the motor cortex, nearly all the giant cells showed splitting or loss of chromatic bodies. None were completely bleached, and the cyto-reticulum was usually distinct.

In *Purkinje's cells* the chromatic bodies were uniformly deficient in size, very irregular in shape, and often greatly reduced in number.

Case III.—*Pyæmia.*—A well developed male infant was delivered by forceps, deeply asphyxiated, April 11, 1897. It never fully recovered from the asphyxia, being always feeble but nursing well, till on April 14th vomiting began. April 15th, there were hemorrhages from the naval and mouth, and "coffee-ground" vomitus; temperature 99.4°. These symptoms continued with a temperature 102.2°, when on April 17th, one wrist and hand became swollen and tender. On April 18th, the stools were tarry, and several indurated spots on the skin were noted. On April 19th, it died, previous temperature not taken.

Autopsy 6 hours post-mortem. The naval was sound. The right clavicle and shoulder joint, left forearm, occipital protuberance, both iliac bones and muscles, and left knee joint, were the seats of extensive abscesses, containing thin serous pus in which were large numbers of streptococci.

Microscopical examination. Lang's fluid.

There were everywhere evidences of post-mortem change consisting in nuclear chromatophilia, ragged granular aspect of chromatic bodies, and extensive vacuolation. The changes were extreme in the cortex, but slight in the medulla.

In the *cord* and *lower medulla* most of the large cells presented well-formed but, as is normal at this age, rather faint chromatic bodies. A few showed beginning central chromatolysis. Above the XII nucleus, especially in the deeper areas, most of the cells showed distinct powdering or complete loss of perinuclear or peripheral chromatic bodies. In some of the smaller cells neither network nor bodies could be seen. In this region cadaveric processes did not seriously interfere with the estimate of the above lesions.

In the *cortex* most of the cells contained considerable chromatic substance, but it was uniformly granular and distorted by vacuoles, as a result of decomposition. *Purkinje's cells* at this age are very small, and in this case they were entirely lacking in chromatic bodies.

Case IV.—*Diffuse Phlegmonous Inflammation.*—Male, 40 years. February 1st received a cut on the toe, which failed to heal. February 10th, he had a chill, with headache and vomiting, and was prostrated for a day, after which he went out and drank to excess. February 13th he noticed pain and swelling in the knee joint and was again prostrated.

On admission February 18th, there was gangrene of left great toe, acute arthritis of the knee joint, and diffuse cellulitis of the thigh. Feb. 19, temperature 105°, about which point it remained. Incision had no effect in limiting the inflammation, although large quantities of pus were evacuated at various times. February 28th, the patient developed delirium and stupor which persisted till death. The general septic condition was extreme during the last three weeks of the illness and the temperature remained about 105° till death, March 25th.

Autopsy 22 hours after death. Body emaciated. There was gangrene of foot, purulent arthritis of knee, and the muscles of the thigh were largely obliterated by an enormous sacculated pus cavity. There were no gross visceral lesions of importance.

Microscopical examination.

In the *cord*, most of the cells contained the usual number of chromatic bodies, but in a considerable number they were partly subdivided, and in some were finely powdered and, in a few segments, usually perinuclear, were lacking. The cyto-reticulum remained.

In the *IX, X and XII cranial nuclei*, most of the cells showed many well-formed chromatic bodies rather faintly staining. Many deeper cells, however, contained only

two or three well-formed chromatic bodies, the remainder of the cell body being bleached. A few cells were entirely bleached.

In the *olives* and *external arcuate nuclei* the chromatic substance was granular but abundant.

In the *motor cortex*, advanced lesions were rather rare, but some of the giant cells exhibited marked changes, the centres being bleached, the peripheries containing a ring of granules, and persisting chromatic bodies being markedly subdivided. The chromatic network of the cortical arkyochromes was often irregular, granular, and partially faded.

The majority of *Purkinje's cells* presented ragged subdivided chromatic bodies, often very deficient in number. Some cells, however, contained well-formed bodies in normal number and arrangement.

No distinct nuclear changes could be detected in the cells in this case.

Case V.—*Pulmonary Tuberculosis. Tuberculous Nephritis. Acute Cellulitis.*—Male, 35 years. Had suffered from cough and dyspnœa for one year, and œdema of legs for two weeks. September 18, 1896, temperature 101°. Signs of tuberculosis of both lungs. Urine, s. g. 1022. No albumen. September 23d, was delirious, temperature 102°. September 24th, a large diffuse phlegmon developed in upper right arm; delirious; temperature 105°. September 25th, urine moderately diminished, slightly albuminous; temperature 105°. September 27th, delirium and coma; involuntary stools; temperature 102°. September 28th, died; temperature 108°.

Autopsy four hours after death. There were many old and fresh tubercles in both lungs. No pneumonia. A few small cavities. Many miliary tubercles were scattered throughout the kidneys of which the surface was smooth, capsule free, and markings very irregular. The soft parts of the upper arm were extensively infiltrated with pus. The pia was very œdematous.

Microscopical examination. Lang's fluid.

Throughout the *medulla* there is extreme chromatolysis. In the *nuc. XII*, the chromatic bodies are reduced to fine granules or appear as irregular masses limited to the sides or poles of the cell, while some of the cells are moderately bleached. Most of the superficial cells throughout the floor of the fourth ventricle are in the same condition. In the *nuc. X*, *IX*, *VIII*, *V*,

IV, *III*, many cells are entirely bleached, but most of them retain a little granular chromatic detritus. In some deeper lying groups of cells there are no traces whatever of chromatic substance. Usually the cyto-reticulum is distinctly visible. In the cerebellum *Purkinje's cells* are either completely bleached or retain a very few slender chromatic bodies. In the *cortex* the larger cells show very little chromatic substance and some are entirely bleached. In the smaller arkyochromes the chromatic reticulum is usually distinct. In all regions the nuclei contain many small secondary nucleoli.

Summary of Observations on Cases of General Sepsis.—In the foregoing cases of general septicæmia, considerable alteration in the chromatic structure of the nerve cells was observed in each instance. These lesions were very irregular in degree and distribution, some regions, especially the cord, cerebellum, and cortex being often very slightly affected. The medullary nuclei were most seriously damaged. There appears to be a fairly constant parallel between the grade of chromatolysis and the severity and duration of the toxæmia and the height of the temperature. That local conditions have a determining influence in the occurrence of these lesions appears from the fact that adjoining nuclei and contiguous cells were very differently affected.

Tetanus.—Most of the studies of the lesions of the central nervous system in tetanus, by means of Nissl's method have appeared within the past two years and the evidence presented is so fragmentary and incomplete that it is at present impossible to determine what special cellular lesions are to be referred to the action of this particular toxæmia.

The first studies of the cellular changes in experimental tetanus were reported by Beck,[169] who examined the cord of two rabbits, dying four days after inoculation with a culture of tetanus. The examination, evidently conducted

with care and judgment, indicated as the cellular lesion referable to the infection. 1st. Swelling of the cell body and separation of the chromatic masses. Often the chromatic bodies were swollen or apparently fused together. 2d. Very often the cells showed a partial peripheral loss of chromatic substance, which the author refers to a degenerative process limited to the area of origin of the axis-cylinder process. 3d. In one of the rabbits the changes were more advanced and most of the cells were swollen, the chromatic structures had largely disappeared, and the cell body stained diffusely blue.

Beck was not convinced that any of these changes were specifically related to tetanus, but regarded them as very similar to those noted by other writers in experimental toxæmias.

Marinesco[170] killed three guinea pigs in rather short periods by injection of tetanus toxine, and examined the cords by Nissl's method. There were numerous hemorrhages in the gray matter. The chromatic bodies were thinned and shortened, and sometimes reduced to a series of granules scattered irregularly throughout the cell body. Occasionally there was peripheral chromatolysis. In advanced stages the chromatic bodies disappeared entirely. The achromatic substance was diffusely stained, and some cells appeared quite homogeneous and darkly stained. In the earlier stages of the toxæmia, very slight alteration could be noted.

Claude[171] produced a subacute myelitis with cachexia, by injections of tetanus toxine, killing the animal after six weeks, but it does not appear that the condition induced could be considered a fair example of experimental tetanus.

Courmont, Doyon and Paviot[172] report the examination

of the cords of three guinea pigs, dying 12 hours, and 9 and 10 days after receiving injections of tetanus toxin. Some of the cells of the anterior horns were found transformed into "deep blue masses" but no other changes were observed. In the cord of a normal guinea pig similar cells were found.

In the cords of three dogs dying five, six, and fourteen days after the injection of tetanus toxine, the anterior horn cells were found entirely normal. On these data the authors deny that tetanus produces any cellular lesions in the spinal cord and attempt especially to discredit the observations of Marinesco and Claude.

Unfortunately the sections in these cases were cut by a razor.

In June, 1898, they presented before the Paris Society of Biology,[172] microscopical specimens claimed to demonstrate the following conditions:

1. In the cords of five dogs suffering from tetanus, "tetaniques," there were no appreciable cellular alterations.

2. In the cords of guinea pigs killed during the period of localized spasms, cellular lesions were present but they were scattered and bilateral, and showed no relation to the seat of the spasms.

3. In the cord of a guinea pig cured of tetanus and killed on the forty-fifth day, the lesions were much more intense than in the preceding cases and affected almost all the cells.

The importance of these observations it is impossible to estimate in the absence of a detailed report, which is promised, in a later number of the same journal (July, 1898).

Goldscheider and Flatau[173] have reported an extensive study of the changes induced by tetanus on the spinal

stichochrome of the rabbit. These changes were found to be uniformly present and consisted in swelling of the nucleolus, cell body, and chromatic masses, followed by granular disintegration of the chromatic bodies. The simultaneous injection of anti-toxine retarded both the appearance of symptoms and the occurrence of changes in the ganglion cells. They believe that a strict parallel between the cellular lesions and the symptoms following injections of tetanus toxine is not to be found. A close examination of the details of their report fails, however, to show that there is any serious discrepancy between the grade of cellular change and the severity of symptoms, although the parallelism is not uniformly maintained at all stages.

Pechoutre[174] found, in rabbits killed four days after injection with cultures of tetanus, the same lesions in the anterior horn cells as described by Beck, and Goldscheider and Flatau.

Hunter[175] examined the spinal cord in two cases of rapidly fatal (24 hours) tetanus. In one he noted a disappearance of the chromatic bodies, and a uniformly homogeneous appearance of the ganglion cells.

In the second case, complicated by extensive pneumonia, the ganglion cells of the cord appeared normal.

It does not appear that the author examined the cells of the medulla or brain in either case, a failure which forbids the drawing of any deductions from these cases, regarding the cellular lesions of tetanus in the human subject.

Goebel[177] reports the examination of the anterior horn cells in a case of tetanus in the human subject. In these cells the nucleus had often lost its outline while the cell body remained normal. Many cells showed great irregularity in form and arrangement of the chromatic bodies,

while some had lost their processes and nuclei, and were reduced to a mass of pigment grains in which only traces of the chromatic substance could be detected.

Goldscheider and Flatau[176] describe the changes in the ganglion cells of the cord in two cases of tetanus. In one, the course of the disease was prolonged to five days, and the changes in the cells consisted in almost complete disappearance of chromatic bodies. The nuclei was lightly but diffusely stained, the nucleoli were not swollen, but rather reduced in size. The patient had few convulsions, and the ante-mortem temperature rose to 39.9° only.

The second case was more rapidly fatal, with severe convulsions. Ante-mortem temperature not stated. Here the cellular lesions consisted only in swelling and partial bleaching of the nucleolus, and in swelling of the chromatic bodies, without distinct bleaching.

Westphal describes similar changes in the anterior horn cells in a more protracted case of tetanus. (Fort der Med., 1898, p. 483).

The writer's series includes one case of tetanus. The patient was a boy of 19 years. The duration of his entire illness was five days; of severe symptoms, three days. The temperature was but slightly elevated until shortly before death when it rose to 107°. The tonic spasm was neither very severe nor continuous, but the fatal termination was marked by several severe general tonic and clonic convulsions. The mind was not greatly affected until the end when, between the convulsions, the patient remained comatose or delirious.

Autopsy one hour after death. There was noted a characteristic bluish discoloration of the gray matter throughout the brain and cord. There were a few ecchymoses on the outer edge of the optic thalamus. There was considerable œdema, but no hyperæmia of the pia. The viscera showed the lesions of the "status infectiosus." The brain and cord were fixed in 97 per cent alcohol. The most marked cellular changes were found in the *cortex*, and consisted in uniform and usually complete

chromatolysis, without distinct alterations in nucleus or achromatic substance. These changes affected especially the archystichochromes and giant stichochromes, nearly all of these cells presenting an appearance quite indistinguishable from that seen in cases of sunstroke and mechanical obstruction to cerebral circulation. In the *medulla* the superficial nuclei showed very slight but general chromatolysis, but the deep nuclei were much altered, many showing complete chromatolysis and marked eccentricity of nuclei. Many *Purkinje cells* showed advanced chromatolysis, others exhibited moderate granular subdivision of chromatic bodies, especially marked in the peripheries and in the dendrites. The *spinal stichochromes* nearly all showed evidence of chromatolysis. In some instances the chromatic bodies appeared swollen and pale as described by Beck. Swelling of the nucleolus was not noted as a distinct feature. Many spinal stichochromes were reduced to the homogeneous appearance characteristic of the cortical cells. The capillaries were everywhere distended with blood and a few minute extravasations were found in the floor of the fourth ventricle. To this general condition the writer believes the cellular lesions are partly referable.

From the evidence at hand, it appears that the earliest cellular lesions in tetanus consist, as originally described by Beck, in swelling of the chromatic bodies, and cell body, and probably also of the nucleolus; that these initial changes are rapidly followed by progressive chromatolysis which may reach an extreme stage without serious alteration of the achromatic substance or nucleus; that these lesions are of rather irregular distribution, being more uniform and intense in the brain than in the cord, and with the possible exception of the early stages, the changes are not specific of the disease.

The writer cannot agree with Goldscheider and Flatau in their supposition that the stages of extreme chromatolysis are referable to febrile disturbances, nor does the failure of some writers to find cellular lesions in the spinal cord in tetanus seem to diminish the importance of the

considerable number of positive results now available. The chief imperfection in previous studies of this condition lies in the failure to examine the entire central nervous system, as the writer's case indicates that the chief cellular lesions are located in the cerebral cortex and medulla.

Hydrophobia.—The cellular lesions demonstrable by older methods in hydrophobia have been fully described by Schaffer[178] and others, while the subject of the pathology of rabies has been ably reviewed by Hogyes[179].

Nagy[180] was apparently the first to employ Nissl's method in this study. During the first four days after infection with rabies in animals, Nagy found that the chromatolytic changes in the cord and brain were not extreme nor were all portions of the cell affected. With the onset of fever, and nervous symptoms, (fifth to seventh day) the changes became general and pronounced. In the stage of paralysis, many completely degenerated cells were found throughout the brain and cord. The changes were most advanced in that part of the cord to which the virus first gained access, as in the lumbar cord when the infection occurs in the sciatic distribution. The lesions described consisted in granular disintegration of the chromatic bodies, followed by homogenization of the cell body, vacuolation, loss of nuclei and processes, and terminal atrophy.

Later, Nagy[181] found that the administration of antirabic serum prevented both the symptoms and the changes in the nervous system following infection with the virus.

Babes[72] has described in hydrophobia experimentally induced in rabbits, extreme stages of chromatolysis, deep staining of the achromatic substances, vacuolation, and rupture of dendrites. In some cells peculiar spindle-

shaped or polygonal areas in the cell body were marked off by clefts and fissures. In the nuclei he observed the loss of nuclear membrane, compression by perinuclear vacuoles, swelling and disappearance of nucleolus, and granular disintegration of all nuclear elements.

Sabrazes and Cabannes[182] have examined by Nissl's method the cervical cord of a case of rabies in a man, 37 years of age. The lesions were most marked in the posterior horns and posterior median portion of the anterior horns. Most of the cells in these regions were completely bleached and had lost their processes. In the anterior horns a variety of the earlier stages of chromatolysis were noted, and nuclear changes were prominent.

The present series includes one case of hydrophobia in the human subject. The patient was a girl aged 19 years, who died four days after the development of the disease with very typical signs of this malady. It was impossible to determine the period of incubation. The cerebral symptoms were very marked throughout the illness, the delirium being violent and terminating in coma. Twenty-four hours before death the temperature, previously little elevated, rose to 105°.

At the autopsy, eight hours after death, the viscera presented the usual changes of the "status infectiosus." The gray matter throughout the central nervous system exhibited in an extreme degree the deep cyanotic color, which is characteristic of both hydrophobia and tetanus. There was also marked congestion of the larger veins of the central nervous system, but no ecchymoses were discovered. Intra-peritoneal and intra-meningeal inoculations from the medulla, made by Dr. Chas. Norris, reproduced the disease in typical form in several series of animals.

Microscopical examination. (Van Gehuchten's fluid, 22 hours. Alcohol).

The cells throughout the *spinal cord* and *spinal ganglia* showed uniform diffuse chromatolysis more marked centrally, often with eccentricity of nucleus. The nucleoli were usually much swollen; the nuclear membrane usually invisible in specimens stained by methylene blue alone, but sometimes demonstrable, in swollen condition,

by erythrosin. The achromatic envelop of the spinal stichochromes stained rather deeply with methylene blue. The borders of the cells and processes were often ragged.

Throughout the medulla the lesions were of the same character, but more intense. All the large stichochromes were extensively altered. The raggedness of the cell borders and processes, the loss of nuclear membrane, and the apparent destruction of the underlying cyto-reticulum were very distinct characters in many of these large medullary stichochromes.

In the *cortex* there was a uniform but not extreme loss of chromatic substance, these regions being considerably less affected than the medulla and cord.

In the cells of the *motor cortex*, there was considerable subdivision and irregularity of the chromatic bodies and network, most advanced about the nucleus and giving these cells, in sections 10 μ in thickness, a somewhat diffusely stained appearance. A similar condition rather more marked was observed in the *Purkinje cells*. Vacuolation of the nucleoli was an extremely pronounced change in nearly all the nerve cells throughout the central nervous system.

Besides the cellular lesions the features of the case were the extreme congestion of the gray matter, everywhere accompanied, especially in the medulla, by many small hemorrhages. There was no distinct circumvascular infiltration with round cells.

Bubonic Plague.—In experimental pest (bubonic plague) Babes[172] found very extensive cellular lesions, consisting in complete chromatolysis, vacuolation, destruction of the peripheral portions of the cell body, and loss of nuclear membrane. Bacilli were often seen within the cell body. The lesions varied with the strength of the injected material. In very rapidly fatal cases, the changes were limited to the cells and were usually of less advanced type. In slower cases, vascular changes became prominent, and cellular lesions had progressed further.

Lugaro[183] has also reported and fully described, in the same infection experimentally induced in animals, extensive lesions in the chromatic and achromatic substance and in the nuclei of the nerve cells, very similar to those described by Babes.

In young children dying with or without fever from the toxæmia of *acute intestinal lesions*, Muller and Manicatide[184] found many advanced changes in the nerve cells. These consisted chiefly in swelling, irregularity in outline, and partial or complete bleaching of the chromatic bodies. In some foci the cells had lost their normal outlines and dendrites were missing. Nuclei and nucleoli were often misplaced and the nuclei usually stained darkly. The lesions were found in both brain and cord. The authors considered them in no respect specific.

In *leprosy* Babes[172] has verified Soudakievicz's domonstration of the *bacillus leprœ* in cells of the spinal ganglia and anterior horns, and describes the appearances of the cells harboring these germs. In many instances the infected cells were very little changed, the chromatic structures being practically intact. In other cells there were vacuoles in the protoplasm and the nuclear membrane was sinuous or lost. In still other cells the bacilli lay in a mass of pigment, while the cells had completely lost all chromatic bodies, were extensively vacuolated, and the nuclear membrane had disappeared.

Pernicious Malaria.—In a case of pernicious æstivo-autumnal malaria, the nervous system was examined by Nissl's method.

The patient, male, 64 years, without previous illness, began to suffer from mild, irregular chills and fever October 1, 1895. Cerebral symptoms were noted early in the illness, in the form of headache, drowsiness, and occasional stupor. During the three weeks of his illness in the hospital, he remained nearly constantly in mild stupor, broken by periods of partial consciousness or active delirium. Treatment, bromides, quinine, and arsenic. The blood contained an unusually large number of parasites which, however, largely disappeared the day before death, which occurred October 25. The temperature ranged continuously from 101° to 104°, reaching 108° just before the fatal termination.

Autopsy eight hours after death. Some bone lesions probably of syphilitic origin were discovered. Otherwise the lesions were those of pernicious malaria. The brain and meninges were moderately œdematous.

Microscopical examination showed a moderate deposit of malarial pigment in the blood vessels and in their walls. The large cells of the cord and medulla showed a moderate grade of general chromatolysis. In some of the medullary ganglia these changes were extreme and the chromatic substance was reduced to a few fine pale granules or rarely was entirely absent. The appearance of Purkinje's cells was somewhat characteristic in that the chromatic bodies at the bases of the cells was intact and of large size, while in the region of the dendrites they were minutely subdivided or entirely absent. Throughout the cortex the cells showed no marked changes other than a uniform deficiency in quantity of chromatic substance.

In all parts of the nervous system not excepting even the Purkinje cells there was an extensive deposit of yellowish granular pigment of the usual character (not malarial) and distribution.

Section VI.

The Significance of the Chromatic Bodies.

The evidence regarding the significance of the chromatic bodies of Nissl is furnished by the study of their usual morphology, their probable chemical composition, their morphological changes at different periods of the life of the cell, their variations in physiological states, and their behavior under pathological conditions.

The foregoing consideration of some of these topics shows that the chromatic substance may assume a great variety of appearances from a large, granular or partly homogeneous circumscribed mass to a diffuse infiltration of the cytoplasm and possibly also of the nucleus.

This fact, especially when viewed in the light of Held's researches, indicates that we are dealing not with a fixed and formed histological element of the cell, but with a

fluid or semi-fluid chemical constituent, occupying of course a certain space, but well limited by the achromatic elements. The observation emphasized by Lenhossek[188] that there is yet strong uniformity of appearance in the chromatic bodies in similar situations, throughout the vertebrate series, does not tend seriously against this view, for as noted by Lugaro[46] the chromatic substance appears to passively adapt itself to the structure of the achromatic portion of the cell. It is difficult or impossible to find any parallel instance where a distinct histological element of the normal cell suffers such remarkable changes in morphology.

The chromatic substance of the nerve cell appears to be more comparable in these respects to the hæmoglobin of the red corpuscles of the blood or to the pepsinogen of the peptic cells, than to cytoplasm, spongioplasm, nucleus, nucleolus, centrosome, or other recognized histological element of the cell.

The morphology of the chromatic bodies at different periods of the life history of the nerve cell, furnishes evidence of a similar character, and indicates also that the chromatic masses are a feature of the fully developed functionating cell, but are not essential to its partial activity.

Reference has already been made to the observations of Vas[70] that the "Nissl bodies" are wanting in the sympathetic ganglion cell at the seventh month, and are not fully developed until the eleventh year, and to that of Eve[73] who finds that only the vagi nuclei in the rabbit's embryo, 2.5 in. long, contain chromatic masses. In the spinal and medullary stichochromes of new born infants examined by the writer, the chromatic masses were less numerous and much paler than in the adult cells, while Purkinje's cells failed to show any distinct traces of such bodies. In

the senile ganglion cell the increasing deposit of pigment is greatly to the cost of the content in chromatic substance, and at this age, nervous functions are generally less active.

The comparative morphology of chromatic bodies in various vertebrates, in so far as this field has been investigated, indicates that the higher the development of the cell the more abundant and distinct are the chromatic bodies. Colucci finds the same rule to hold among the various cells of the human organism, although he regards the chromatic bodies as fixed elements of the cell.

Comparing the spinal stichochromes of man, the dog, the cat, and the rabbit, with those of the sluggish mud puppy and water moccasin, the writer finds that the motor cells of the more active animals show a greatly superior development of chromatic substance. The extensive study of Levi[189] on the comparative morphology of nerve cells in vertebrates leads to the same general conclusion.

It may, therefore, be readily seen that there is abundant theoretical evidence for the belief that the chromatic substance is principally related to the activities of the cell, and from that standpoint numerous studies have been undertaken to ascertain the behavior of the nerve cell and especially of its chromatic elements in physiological conditions.

Effects of Fatigue Upon the Nerve Cell.

Among the earliest of these studies was that of Hodge.[190] This experimenter resorted to electrical stimulation of the cervical sympathetic ganglion for several hours, allowing short intervals of rest to the animals, dogs, which usually died before the experiment was concluded. He used the ganglia of the opposite side for control preparations. The changes noted consisted in a marked decrease

in the size of the nucleus, with irregularity in its outlines, loss of its clear reticulated appearance, and a darker staining tendency. The cell body was shrunken and vacuolated and the pericellular lymph space was dilated. No observations were reported on the chromatic substances.

About the same time, and with a similar object, Mann[191] studied the change in nerve cells during functional activity. After working dogs to the point of physical fatigue, and later to exhaustion, he examined the cortical brain cells by a method similar to Nissl's. In the normal brain the cells appeared as dark blue bodies on a light background, while in the brain of the exhausted animal, they appeared very pale or quite colorless. This difference in color he refers to the withdrawal of lymph which he supposes is more abundant in the active cell. He further concludes; that during rest several chromatic principles are stored up in the nerve cell, which are consumed during functional activity; that activity is accompanied by increase of size of body, nucleus, and nucleolus, of motor, sensory, and sympathetic ganglion cells, while fatigue is accompanied by a shrivelling of the nucleus and probably also of the cell, and by the diffusion of chromatic material in the nucleus.

Serious errors in the procedures and technics of both Hodge and Mann have been pointed out, greatly lessening the value of their studies.

It is difficult to see any similarity between normal activity of the sympathetic ganglion and prolonged electrical stimulation of this structure, nor does it appear probable that prolonged physical exertion could greatly alter the cortical brain cells of the dog. Nissl[192] therefore thinks that all the unusual appearances seen by Hodge and Mann were artifacts, a criticism rather too severe,

since the trustworthy investigations of Lugaro[200] have demonstrated changes in the volume of nucleus and nucleolus as the result of exhaustion, and several years previously, Korybutt and Daskiewicz[193] after electrical stimulation of the sciatic, had found marked increase in size of the nuclei of the spinal cells giving origin to this nerve.

Vas[70] also faradized the upper cervical sympathetic ganglion of the rabbit for fifteen minutes, and found thereafter that the nucleus was enlarged, eccentric, often bulging from the periphery of the cell. The cell body was increased one-third in size. The perinuclear zone was bleached and poor in chromatic substance, while a ring of large chromatic bodies remained along the periphery of the cell.

Lugaro[200] discredits the importance of these findings, because Vas dissected the ganglia while the animal was still living, thus subjecting it to extreme traumatic influences, while Nissl criticises the use of electricity as a wholly unsuitable means of exciting functional activity in ganglionic cells.

Lambert[194] after exposing the sympathetic ganglia of rabbits and applying galvanism for fifteen minutes, found marked eccentricity of the nucleus. Unfortunately, he killed the animals by hydrocyanic acid.

Levi,[195] after electrical stimulation of the spinal ganglia in rabbits, found no change in the chromatic granules, but found an increase in the size and number of the fine granules staining by fuchsin which lie among the fibrils in the achromatic portion of the cell. He believes also that during cellular activity there is an increase in the size and number of the granules of true chromatin lying about the nucleoli of these cells.

Eve,[193] studying the sympathetic ganglion cells in prolonged activity and in repose, finds that the chromatic bodies disappear, the cell staining diffusely pale blue, after galvanization of the ganglia or their nerve trunks, changes similar to those occurring in the spinal stichochromes after strychnine poisoning. Eve supposes that cellular activity produces acid metabolic products that dissolve the chromatic bodies. He discovered in the nuclei no changes referable to fatigue.

To Magini[196] belongs the credit of calling attention to the electric lobe of the torpedo, as a specially favorable situation for the study of changes in ganglion cells, referable to fatigue. The adult torpedo when killed in a healthy condition reacts with well known violent electric discharges. According to Magini the nuclei of the governing cells of this organ then show, without exception, marked eccentricity, being always drawn toward the electric nerve, while the nucleolus is always found close to the nuclear membrane. When the adult animal dies slowly out of water, it does not discharge electricity, and the nuclei are not found drawn toward the nerve or the nucleoli toward the nuclear membrane. Very young torpedoes do not give electric discharges, and the nucleoli of the rudimentary cells are always found in the centre of the pale nuclei. No references to the chromatic substance was made in Magini's observations. Coggi,[197] who saw these specimens, as well as Valenza[198] and Lugaro, regard this eccentricity of the nucleus as an artifact.

Valenza[198] applied strong faradization to the electric lobe of the torpedo. In the cells nearest to the electrode there was hyperchromatosis of the nucleus and shrinkage of the cell body; in the more distant cells there was swelling of the cell body and hyperchromatosis of the periph-

eral zones. By direct cauterization of the organ there was produced hyperchromatoses of the nucleus and a concentration of chromatic bodies about it.

Valenza found no changes referable to simple activity or repose.

Nissl, 1896,[199] reviewing the results of this line of study up to date, concluded that the morphology of the nerve cell in exhaustion was still undetermined, and that the evidence was still insufficient to show whether the pyknomorphous condition of the cell is the expression of the resting state or the apyknomorphous condition the expression of activity. Since that time there have appeared the careful studies of Lugaro[200] who still fails to discover chromatic changes referable to fatigue. Lugaro excited the cervical sympathetic ganglia by faradic electricity, killed the animals before further manipulation of the ganglia, and carefully observed the changes, resorting to exact measurements of the cell body, nucleus, and nucleolus. His conclusions are as follows: "Activity of the nerve cell is accompanied by a state of turgescence of its protoplasm, while fatigue produces a progressive diminution in size of the cell body. In moderate degrees of fatigue, while the cell body swells, the nucleus does not change its volume. The shape of the nucleus always remains uniform, nor is its position changed, marked eccentricity being just as common in ganglia in repose as in fatigue. When activity is much prolonged, the nucleus undergoes the same changes in volume as the cell body, but less markedly, and more slowly. The quantity of chromatic substance in the cell body varies as an individual character, and in relation to the size of the cell. During the swelling of the cell in activity there is perhaps an increase of chromatic substance, and in the stage of fatigue,

perhaps it fades a little and becomes more diffuse, but it is certain that the great differences in staining power and content of chromatic substance that one sees in cells of the same ganglia cannot be attributed to differences in physiological state. Activity and fatigue may cause changes in the staining capacity of all sorts of cells, but do not change a pyknomorphous into an apyknomorphous cell. Activity determines in the nucleolus an increase of volume which yields slowly to the contrary action of fatigue."

The interesting studies of Pergens[201] on the effects on the retinal cells of strong illumination do not seem to bear directly on this subject. Among other changes, however, Pergens noted a diminished affinity for basic dyes in the nuclei and bodies of the rods and cones.

It will thus be seen that the numerous foregoing studies have failed to establish a connection between the chromatic substance of the nerve cell and its conditions of activity or fatigue, so far as can be determined after direct electrical stimulation.

Nissl's objection that electrical stimulation cannot be substituted for natural cellular activity, but works as a traumatic or chemical irritant, seems most reasonable, and indicates that any such studies should be undertaken on different principles.

Accordingly, Pick[202] has recently devised a method of securing specimens of exhausted nerve cells, which is apparently free from any of the objections raised against previous methods. He exposed the motor cortex of one side in monkeys and cats, applied faradism for one hour, exciting muscular contractions of the limbs of the opposite side only. The fatigued cells examined were those of the cord, and in this region he found that the cells of the

convulsed side presented marked granular subdivision of the perinuclear chromatic bodies, and shrinkage and diffuse staining of the nucleus. Not only were the anterior horn cells affected, but the lesions were most advanced in the cells lying midway between the anterior and posterior horns. This fact Pick regards as further evidence that the anterior horn cells are not directly connected with the cortical neuron but are separated by a second intermediate neuron.

Luxenburg[203] has also recently reported a somewhat similar study leading to very similar conclusions.

If corroborated, Pick's and Luxenburg's results would seem to furnish the long expected evidence that natural fatigue of the ganglion cells is associated with a loss of chromatic substance in the nerve cell.

Superior to all the results obtained by experimentation appears to be the isolated and too little considered observation of Levi,[204] that in *some animals the chromatic bodies disappear from the spinal stichochromes during hibernation.* Such a fact, if corroborated, must carry very great significance concerning the relation of chromatic substance and cellular activity. The writer has made several attempts to secure animals in a state of hibernation, but has so far been unsuccessful.

Relation of the Chromatic Bodies and the State of Nutrition of the Cell.

A further line of investigation has had in view the allied theory that the chromatic bodies are reserve nutritive substances stored in the cell, to be used up during periods of activity, in other words, that they represent the potential energy of the cell. This theory has been rather eagerly accepted by many French writers, and Marinesco[205] has

accordingly suggested the term *kinetoplasm* for the chromatic substance and *trophoplasm* for the achromatic part of the cell.

Numerous attempts have been made to alter the conditions of nutrition surrounding the nerve cell in the hope of establishing a connection between the state of the blood and lymph supply of the cell, and its content in chromatic substance.

Monti's[206] experiments are the first bearing indirectly on this point. He produced multiple emboli of the cerebral vessels by intravenous injection of powdered lycopodium, and found, by Golgi's method, that within a few hours varicosities were produced in the dendrites lying next the small thrombosed vessels, while the dendrites in contact with pervious vessels remained normal. These changes gradually approached the cell body, until, in 48 hours, the cell body began to show alterations.

These experiments were repeated by Lamy,[207] who examined the cells by Nissl's method, and found progressive loss of chromatic substance beginning in the altered dendrites and gradually affecting the entire cell body. These changes were similar to those produced in the lumbar cord by ligature of the aorta.

This latter method of affecting the nutrition of the ganglion cell was first employed by Sarbo[208]. In one and one-half hours after tying the abdominal aorta, the chromatic bodies of the spinal stichochromes were less distinct and their outlines less sharp, while the nucleus stained diffusely pale blue. In 24 hours nearly all cells were affected. The chromatic bodies throughout the cell body and dentrites were broken up into a series of fine particles, although some cells showed apparently normal segments. The nuclei presented characteristic alterations which he

denominated "acute homogenization with atrophy." They stained diffusely deep blue, the nuclear membrane being invisible, and the nucleus appeared to be reduced in size. In some instances the nucleus showed advanced changes while the cell body and dendrites contained nearly normal chromatic bodies. A second form of alteration he describes as "homogeneous swelling," in which the body is enlarged, uniformly darkened, and filled with fine granules. In some cells, also, a process of partial sclerosis affected segments of the body which appeared very dark, as though several chromatic bodies had become fused together. Vacuolation of these altered cells was often marked.

Juliusberger[40] also, compressed the abdominal aorta in rabbits, and at the expiration of 15 to 60 minutes, found a granular disintegration of the chromatic bodies progressing concentrically from the perinuclear zone, or affecting smaller segments only.

Marinesco,[209] repeating these experiments, concluded that anæmia does not always produce similar lesions. As a rule, disintegration of chromatic bodies began in his cases in the dendrites, and progressed toward the nucleus, being well marked usually in six hours. He found many swollen cells. In some instances the chromatic bodies appeared to be massed together and the achromatic portion deeply stained.

The results of these experimental studies are very fully verified in the human subject by the writer's cases of thrombosis of cerebral vessels and cerebral hemorrhage. In no other group of cases was the destruction of chromatic substance so rapid and complete, and it seems reasonable to conclude therefrom that the chromatic structures of these nerve cells are more immediately affected by changes in their blood supply than by any

other influences whose effects upon them have yet been studied.

Moreover, throughout all groups of cases in the present series, there was constantly recurring evidence that previous overaction of the nerve cells, as well as local disorders of circulation, were of prime importance in determining the distribution of the lesions in the various toxæmias.

It would seem also that the demonstration of the close dependence of the chromatic bodies upon the blood supply of the cell had furnished the true answer to the question which Hodge, Mann, Lugaro, and others, had in view. For even if it were possible to induce a state of complete natural fatigue in the nerve cell, it might still be difficult to determine which element of the cell were most concerned with such activity, if the normal sources of its supply were still open. All of these considerations indicate, therefore, that the chromatic bodies constitute surplus nutritive products of the nerve cell, or represent potential energy in the cell.

Against such a view Colucci,[210] however, expresses himself very positively. He finds no reason to suppose that the nutritive function of nerve cells is so entirely different from that of other cells as to require the storage of large masses like the chromatic bodies. He regards it as unreasonable to suppose that a nutritive substance should be found so polymorphous and yet, in similar situations, so orderly and fixed as are the chromatic bodies. For a nutritive substance ought to be found about the nucleus where most work is to be done and not limited to the periphery as in many cells, or found in the dendrites. He calls attention to the fact that there is no uniform quantitative relation between the chromatic bodies and

the achromatic substance, one being abundant where the other is often lacking.

Nevertheless, the consideration of more recent data leads irresistibly to the conclusion that *the chromatic bodies of the nerve cells represent a state of physiological nutrition, and may vary between their full development in the anterior horn cells of the adult lumbar cord and their temporary absence in the cells of the hibernating animal.*

The Functional Capacity of Cells Deficient in Chromatic Substance.

It remains to determine how far the loss of this nutritive material affects the functional activity of the cell.

On this point, it is to be admitted at once that the functions of vital nerve centres may be entirely destroyed without leaving demonstrable changes in the chromatic structures, as in the cases of rapidly fatal poisoning, and in this respect the original expectations of Nissl's stain have been disappointed.

On the other hand, the unbiased observer will admit from the reports of the condition of the cells in the many pathological conditions in which Nissl's method has been employed, that there is a fair general parallel, subject of course to a great variety of limitations, between the extent of the lesions in the chromatic structures and the grade of functional disorder, in the ganglion cells. The exceptions to the above rule are so frequent, however, as to render it equally apparent that the capacity of a cell to maintain a temporary function cannot always be estimated by the condition of its chromatic elements.

Of special interest are the contributions recently made to this subject by Goldscheider and Flatau[211].

These investigators employed two very successful

methods of altering the conditions of the chromatic substance in the anterior horn cells. First, they injected into the ear veins of rabbits repeated doses, .005 to .01 gr., of malonitril ($CN—CH_2—CN$), producing thereby marked symptoms of poisoning, dyspnœa, salivation, convulsions, and paresis, and at the height of the symptoms rapidly restored the animals to apparently their normal conditions by injections of Na sub-sulphate. This latter substance has been shown by Heymans and Masuin[212] to be a direct chemical antidote to malonitril. The chromatic bodies of the spinal stichochromes after the administration of malonitril in poisonous doses, showed irregularities of outline and occasionally subdivision into fine granules. The spindles in the dendrites usually remained normal. The nuclei and the achromatic portions of the cells were diffusely stained. After restoration of the animals by Na sub-sulphate, similar changes in the chromatic bodies were found to persist for some hours although the motor power of the animals was apparently restored.

Secondly, rabbits were placed in a thermostat at a temperature of 45° C. until their internal temperature was elevated to 42° to 44° C., a procedure which induced dyspnœa, great weakness, spasms, and convulsions. In these animals the spinal stichochromes showed a complete absence of chromatic bodies. This change was noted in the periphery of the cell when the temperature of the animals reached 41° to 42° C., and became general when the temperature rose to 43°.

When the animals were allowed to recuperate in the open air for from two and one-half to sixty-eight hours, the anterior horn cells showed a gradual restitution to their normal appearance. In some of the animals there were marked changes in the chromatic bodies, bleaching,

irregularity of outline, and partial subdivision, at a period when the motor power appeared to be completely restored.

From these very interesting data, the authors conclude that the chromatic bodies of Nissl have no vital importance in the nerve cell, and that their relation to the functions of the cell appears doubtful, since they could not say that the alterations observed were always beyond doubt to be regarded as the substratum of the disturbances of function observed in the animals. Yet they consider their experiments to have shown that malonitril and the artificial elevation of temperature induce a disturbance of function, and, if more active, a simultaneous disturbance in the nutrition of the cell. The functional disturbance may rapidly pass off, but the disturbance of nutrition is very slowly recovered from. Both processes begin together, but later proceed more or less independently of one another.

Having observed in August, 1896, throughout the central nervous system of a case of insolation, lesions identical in many respects with those described by Goldscheider and Flatau in the spinal stichochromes of heated rabbits, the writer was lead to repeat those experiments for the purpose of comparing the lesions with those found in sunstroke, and with the further object of carefully comparing the alterations in the chromatic bodies with the grade of functional disturbances observed in the animals.

The importance of the subject may warrant a report of some of these experiments.

Experiment I.—A medium-sized healthy female rabbit, rectal temperature 38.3° C., was placed at 11.45 A. M., in a dry air oven, in which the temperature ranged between 46° and 48° C. It began to breath rapidly at once. After

one hour it lay panting on its side and seemed very weak, although kicking rather actively when prodded. Temperature 41.5°. After one and one-half hours the animal seemed greatly exhausted, being hardly able to stand. The reflexes were markedly hyperæsthetic and breathing was very rapid. At the expiration of two hours the animal was found dead and rigid. Rectal temperature 44° C.

The examination of the viscera revealed much venous congestion of cerebro-spinal meninges, and lungs. The other viscera were notably pale. The blood was very dark and entirely fluid, failing to clot also after shedding.

The central nervous system was examined, after hardening 24 hours in Lang's fluid, by Nissl's method. In the *medulla* all the chromatic bodies of the nerve cells had disappeared, although some cells showed a faintly visible network or a few dark granules in the cytoplasm. Large, clear vacuoles were seen in some cells. The cell bodies looked waxy, staining light blue, their outlines were usually regular. The nuclei were, almost without exception, diffusely stained dark blue. About the nucleoli were often two to five dark granules, while the nuclear membrane was irregularly invisible. In the *cord*, the chromatic bodies of the stichochromes had almost entirely disappeared, the cell bodies looking waxy, swollen, and staining diffusely light blue, the periphery being very pale. In many cells traces of the chromatic bodies could be detected, (1) in the form of very pale ragged masses of the same general shape as in the normal condition. (2) In the form of fine granules scattered through the cytoplasm, sometimes in the form of a network; and (3) as a diffuse discolorization of the entire cell. The dendrites showed an irregular network composed of granules, or occasionally a ragged spindle. The nuclei were very darkly stained, their position was usually central, and they resembled the nuclei of the medullary cells.

Experiment II. Similar in most respects to the first, except that after two and one-half hours, the animal, with

a rectal temperature of 45° C., was removed from the oven and placed in a draught of fresh air, with the expectation that it would recover. Although the symptoms had been rather less marked than in the first case, one hour later the rabbit was found dead and rigid. Post-mortem appearances and condition of ganglion cells, the same as in former case.

Experiment III. Was undertaken to ascertain more accurately the symptoms occurring before death.

After one hour the rabbit's temperature registered 43°. It lay on its side and was unable to stand for more than a few seconds, falling with very marked tremor. The respirations were 320 per minute and irregular. The reflexes were exaggerated. Placed in a draught for five minutes, it seemed greatly recovered, and sat in a normal position, the respiration falling to 200. After three and one-half hours, the temperature of the oven being 45°, the animal's temperature registered 44.6°, and it was again placed in a draught. At 3 hours, 45 minutes, temperature 43.6°; at 4 hours, 41.6°; at 4½ hours, 39°. The fresh air very rapidly improved the animal's appearance, the respiration became nearly normal, and motor power seemed also normal. The reflexes were still exaggerated. It was again placed in the oven and its temperature raised in one hour to 45°. All the symptoms then returned, spasms of the limbs could readily be elicited, there was one short period of general clonic convulsions, later two general tonic spasms, ending in death, six hours from the beginning, with rectal temperature 45°.

The post-mortem appearances of the viscera and the condition of the ganglion cells throughout the central nervous system did not differ materially from those described in experiment No. 1. These experiments were repeated in a slightly altered form on four other rabbits, without eliciting any new facts in regard to the relation between the symptoms exhibited by the animals and the condition of the ganglion cells of the central nervous system. It may be noted in passing that the amphophilic

network demonstrated in the cells of the liver and kidney of normal animals was partly or completely destroyed in a degree quite comparable to the changes observed in the nerve cells.

The experiments, therefore, bear out completely the conclusions of Goldscheider and Flatau, that artificial elevation of temperature very rapidly distorts or destroys the chromatic structure of the ganglion cells of rabbits.

A further set of experiments was conducted upon rabbits to determine how far the nervous function of these animals could be restored by prompt resuscitation after exposure to high temperatures, and in order to ascertain the condition of the ganglion cells in the resuscitated animals.

The following report will serve to illustrate four very similar experiments of this order:

A medium-sized black field rabbit, temperature 38.5° C, was placed in the oven, temperature 45.7° C at 10 A.M. At 11 A.M. the temperature of the oven was 47° C, that of the rabbit 42° C. The usual symptoms were observed, the animal lay panting but kicked vigorously when prodded. At 12 M. the temperature of oven was 48° C, that of the rabbit 43° C. Dyspnœa was now very marked, and the animal was hardly able to sit up, and it was now placed in a draught for 15 minutes. At 12.45 P.M. the temperature of the oven being 52° C, and that of the rabbit 45° C, it was noted that the respirations had fallen to 134, and shortly thereafter to 100, when breathing became irregular. The circulation was now very feeble. The reflexes were not exaggerated. The animal lay on its side, and could not hold up its head. It was bathed in water for 10 minutes, as death appeared to be imminent, and improved considerably. At 1.15 P.M. its temperature was 44°C. At 2.15 it was running about the room and was difficult to catch. When carefully watched however, it appeared to be partly

blind, as it repeatedly ran into the wall. The reflexes were now extremely exaggerated, the slightest touch starting a violent general tremor with occasional spasms. Circulation and respiration appeared normal. Temperature at 2.15 P.M. 40° C. At 2.40 P.M., temperature 39° C, the animal was rendered unconscious by a light blow on the head and was then exsanguinated, two hours after the last exposure to heat. The examination of the central nervous system revealed the same changes as noted in the previous experiments. In three other experiments the animals were allowed to recover for three and four hours after the last exposure to heat, but no distinct improvement in the nervous condition of the animals and no restitution of the cellular lesions in the nervous system were noted. Having noted, as did Goldscheider and Flatau, a considerable restoration of function in cells presenting extensive alteration or destruction of chromatic structures, it was thought unnecessary to continue these experiments further.

The writer's observations accord with those of Goldscheider and Flatau *with the exception that in the above experiments the cellular lesions were accompanied by a persistent loss of functional capacity as indicated especially by the persistent hyperæsthesia of the reflexes.*

It is, therefore, impossible to fully agree with the claim of the above investigators, that the functions of these extensively altered cells are entirely normal. Moreover, it might well be urged that it is impossible to detect in rabbits many finer disturbances of nervous function such as may be fully recognizable in man, and may, by analogy, be supposed to exist in animals thus treated.

It is well known that patients recovering from sunstroke, a condition in which the writer finds cellular lesions very similar to those in heated rabbits, are very liable to suffer from a variety of functional nervous disorders, including tachycardia, paralysis, and sudden death, and this fact must

stand as evidence that ganglion cells once affected in this way, are not immediately restored to full functional activity. It must be accepted, however, that a considerable grade of functional capacity may remain in cells showing extensive lesions of the chromatic substance.

Further than this the present state of our knowledge does not permit any deductions to be drawn concerning the relation between disordered function and altered structure of the nerve cell. It remains for future investigations to determine, either from peculiar characters of the chromatolysis, or, as seems more likely, from changes in the nucleus and achromatic portion of the cell what degree of functional capacity may remain in cells showing various grades of chromatolysis.

Section VII.

Effects of Hyperpyrexia in the Human Subject.

The effects of artificial elevation of temperature upon the ganglion cells in rabbits naturally raises the suspicion that many of the cellular changes now attributed to various intoxications and infections are referable solely to the pyrexia attending these conditions and do not accurately measure the action of the circulating toxic agent.

Moxter[213] studied the effects of elevation of temperature in rabbits caused by puncture of the medulla after the method of Aronsohn and Sachs. (Ffluger's Archiv., 37, 1885).

In one rabbit whose temperature rose to 41.5°, 23 hours after a second operation, many of the cells of the anterior horn of the cervical cord showed advanced chromatolytic lesions. In four other rabbits killed after repeated operations on successive days, and in which the temperature

varied between 38° and 41° no changes were found in the cells of the cord. The author concludes from this rather meagre evidence that simple elevation of temperature is sufficient to induce chromatolytic lesions in the nerve cells.

Goldscheider and Flatau[214] reach the same conclusions from observing in cases of tetanus and scarlatina, cellular lesions similar to those seen in rabbits heated in the oven.

Throughout the present series of cases the writer has observed a uniform fading of the chromatic substance in addition to other lesions in many cases attended with high fever.

Among such cases may be mentioned—the case of tetanus; Case VII of subacute leptomeningits; Case II of pneumonia; the case of general burns; and the first two cases of sunstroke.

The following case also is believed to be of special interest in this connection. (It will be fully reported later by Doctor Robert Abbe, to whom the writer is indebted for the reference to the nervous system).

Sudden Death after Osteotomy.

Female, five years old. Osteotomy of both tibiæ was performed for bow legs at 3 P. M. July 8. The anæsthesia, by ether, and the operation, lasting thirty minutes, were uneventful and the child was put to bed in apparently good condition. At 6 P. M. the temperature was found to be 103°. At 7 P. M. 105°; at 12 P. M. 106°; at 3 A. M. 109°; at 5.30 A. M. the child died, ante-mortem temperature not taken. During the last nine hours the pulse became very rapid and the respiration rose to 40 per minute, but there was no cyanosis. There were no convulsions or paralysis, no subjective complaints, and no other noteworthy symptoms. The temperature at death was probably 110°.

Autopsy ten hours after death.

The thymus was considerably enlarged, measuring 4 x 5 x 1 cm. There were general evidences of old rachitis. The lymphatic system appeared normal. The lungs were intensely congested and slightly œdematous. The

other viscera were moderately congested. No other lesions were discovered.

Microscopical examination. Formalin 10 per cent.

The question of embolic processes in the lungs and other viscera has not yet been determined, and in any case can prove only of secondary import in the purpose for which this report is now made.

In the *lumbar cord* nearly all cells are extremely faint, the chromatic bodies having faded uniformly without apparent subdivision. They sometimes appear swollen. The nuclei are coarsely granular, and the nucleoli swollen and composed of coarse refractive granules. Some cells are composed exclusively of coarse, faintly bluish stained granules. In a few cells, the perinuclear chromatic bodies persist, but are swollen and considerably faded. The cyto-reticulum is invisible.

In the *cervical cord* the changes are similar but slightly less marked.

In the *spinal ganglia* extreme alterations of the same general type were noted, but the chromatolysis was more marked in the perinuclear areas of the cells; while along the peripheries there was a considerable remnant of chromatic substance but no distinct bodies.

Throughout the *medulla* nearly all the cells are extensively bleached. Many are entirely lacking in chromatic substance. In some the chromatic bodies are still preserved but they are extremely pale, so that their outlines are barely distinguishable. The nucleoli are swollen and very pale. Purkinje's cells are least affected. Most of them show a few distinct chromatic bodies limited to the base or periphery of the cell. The other bodies are either invisible or extremely thin and pale.

In the *motor cortex* there is uniform and extreme reduction in chromatic substance in all the cells.

The above case must be regarded as a specially favorable opportunity of ascertaining in the human subject the effects of high temperature uncomplicated by other toxic influences. The extreme loss of chromatic substance in all regions of the central nervous system can be attributed, it would seem, solely to the pyrexia. Ether does not produce such changes in animals, nor such symptoms in the human subject, and embolic processes could hardly have reached such general distribution as were shown by the lesions in the nerve cells.

The chromatolytic process was here somewhat different from that observed in sunstroke, and in heated rabbits, for the chromatic bodies in both the latter conditions suffered much granular subdivision before disappearing, while in this instance, they appeared to fade usually without granular subdivision.

It is important to note that the nuclei of all the cells in the tissues examined stained with diminished intensity by methylene blue.

From the evidence thus reviewed it seems probable that in cases attended with extreme pyrexia, *i. e.*, above 107° F., extensive bleaching of the great majority of ganglion cells in the central nervous system may indicate only the effects of the febrile process and not those of an associated toxæmia.

On the other hand, the present series offers several instances which prove beyond a doubt that extreme pyrexia lasting many hours may fail to induce such general chromatolytic changes in the ganglion cells. Among these may be mentioned Case IV of pneumonia, and Case III of sunstroke, in which there was high and continuous pyrexia, but extreme examples of chromatolysis occurred in isolated foci only and many cells remained intact.

On the other hand, also, the cases of the present series in which prolonged high temperature of 105° to 106°, failed to induce extreme grades of chromatolysis of general distribution are rather numerous and one is forced to conclude that the ordinary temperature of infectious diseases plays only a limited and secondary part in the chromatolytic changes observed in these conditions.

It is hardly necessary to add that an observation of ante-mortem temperature is an essential in the study of clinical material by Nissl's method.

Section VIII.

General Character of the Lesions in Nerve Cells.

The confusion which has resulted from the use of a variety of terms to designate the same change in the chromatic bodies of the nerve cells, renders it very desirable that a uniform nomenclature should be employed in the description of these lesions. Unfortunately for this end, the different stages of the process of chromatolysis and the effects of different reagents give extremely varied pictures of these changes, although as the writer believes, the process is always essentially one and the same, consisting in a diminution of volume by one means or another of the mass of chromatic substance.

The chromatolytic process is frequently, if not always, initiated by a *preliminary swelling of the chromatic body*. The exact nature of this change is not known, nor has its presence in suitable conditions invariably been noted. Examples of this stage are best demonstrated in the early periods of infection with tetanus, and in artificially heated animals.

Either with or without the preliminary stage, the chromatic substance begins to disappear from the mass. If the change proceeds slowly the chromatic body diminishes uniformly in size, and in the last stages appears as a slender and pale spindle or granule. Such appearances are common in slowly fatal cases of obstruction to cerebral circulation, and the change may be designated *as uniform diminution in size of the chromatic body*. When the lesion advances more rapidly several points in the chromatic body may appear bleached, the mass may be partly subdivided or reticulated, and the process may be designated *as uniform subdivision of the chromatic body*. Many such cells may be seen in the chronic toxæmias.

In many severe and acute lesions the process seems to affect all portions of the chromatic body, reducing it to a series of granules, which at first indistinctly outline the original mass, later are found diffusely scattered throughout the cytoplasm and giving the cell a peculiar dusty aspect. This appearance may be designated as *the granular subdivision of the chromatic body*. The distinctness of the granular appearance, at least in the early stages, will depend much upon the fixing agent employed.

All stages of such alteration may be followed in most cases of acute poisoning.

The final stage of the chromatolytic process may leave the cell entirely lacking in chromatic substance, and showing on close inspection only the original cyto-reticulum which is usually demonstrable by methylene blue. This stage is usually spoken of as *complete simple chromatolysis.*

Whatever variation there may be in the intermediate stages, the end results of simple chromatolysis are usually identical. The writer has been unable to find upon close scrutiny any essential difference in the structure of the badly altered cells in sunstroke, alcoholism, thrombosis of the basilar artery, cerebral hemorrhage, the acute and chronic toxæmias, and most of the cells in tetanus.

In most of these cases the complete bleaching of the cell has been reached without demonstrable changes in the cytoplasm or nucleus.

It is usual for the chromatolytic process to affect exclusively the perinuclear zone (*central chromatolysis*), or the peripheral areas (*peripheral chromatolysis*), or, at times, one or more segments of the body (*circumscribed chromatolysis*). Often all the chromatic bodies are uniformly subdivided, occasionally only the dendritic masses.

The well known appearance of the cell affected by

central chromatolysis and eccentricity of the nucleus has been aptly termed by Van Gieson the "axonal degeneration."

During the process of chromatolysis, however, other changes are often described, affecting the achromatic substance and the nucleus. Thus a *diffuse staining of the achromatic substance* is often reported in the examination of the cells, pointing either to a diffusion of the chromatic substance into the achromatic, or to a chemical alteration of the cytoplasm. Nearly every pathological specimen contains cells of this appearance, yet it is far from certain that the achromatic substance ever really exhibits an increased affinity for methylene blue. Without insisting that such is invariably the case, the writer is convinced that the vast majority of these appearances are artificial, resulting from incomplete decolorization, an unusually thick section of cell body which may occupy the entire depth of the cut section, and from the diffused blue refraction of finely subdivided chromatic bodies. See Plate IV, Fig. 2. Such cells are very striking in the cords of heated rabbits, but the diffuse bluish stain disappears in very thin sections.

Likewise nuclear chromatophilia in thin sections disappears or resolves itself into the presence of numerous fine granules in the intranuclear network.

The significance of vacuolation has already been discussed.

It is very probable that vacuoles may form in moderate numbers and of small size from vital patholgical processes, in which case their presence indicates a true degenerative change in the cell body.

Rupture of dendrites has often been referred to as a vital pathological process, but it is far from clear that the

condition results from any other influence than traumatism, applied either in extracting the brain and cord from the body, or resulting from the shrinkage of tissues during the hardening process.

The finer changes in the achromatic substance it is impossible in the present state of our knowledge to describe accurately. In the majority of cells that have lost their chromatic bodies a delicate cyto-reticulum remains visible. In many of the severe toxæmias and especially in the acute infections of the nervous system, as tetanus, hydrophobia, myelitis, etc., this cyto-reticulum may be found to be irregular, coarsely granular, distorted by vacuoles, or may become invisible. In some instances the coarse granules may show slightly altered staining reactions and refrangibility, and in some of the writer's cases, these granules seemed to approach the character of the ordinary yellowish pigment deposit.

The *formation of clefts and fissures* is a distinct feature of the lesions of the achromatic substance as seen in various conditions. These changes, while of great interest, as bearing on the structure of the ganglion cell, have not yet received any explanation.

The entire cell body may be found to be slightly *swollen*, especially in the early stages of chromatolysis. In simple chromatolysis no changes in the size or contour of the cell body is ordinarily found. In most human subjects dying from general diseases, some cells exhibit *irregularity in outline* which indicates a true degenerative process, affecting all elements. The possible effects of reagents must here, of course, be constantly recognized.

In lesions of longer standing, the cell body may be markedly *shrunken*, its *outlines rounded*, the *dendrites may disappear*, the chromatic substance is entirely wanting,

and the *cytoplasm* may appear uniformly and coarsely *granular*.

A considerable variety of nuclear changes has been described.

The nucleus is often *shrunken*, but it is difficult to see what vital process can induce such a change, and its significance is as yet uncertain.

A peculiar appearance sometimes encountered, and depicted in Plate VI, Fig. 5, is the gathering of granules and rods of chromatic substance about one side of a shrunken nucleus. This change also is without known significance. The *nuclear membrane may be invisible* in specimens stained by methylene blue. In some of these cells a counterstain by erythrosin may demonstrate a faint persisting membrane, or, in other instances, this structure seems to have entirely disappeared.

The intra-nuclear network is often replaced by a series of pale granules, very irregular in size and position. The character and location of these granules is fully demonstrated by erythrosin.

Nuclear chromatophilia the writer must refer to the presence of many of these fine granules or to an underlying stratum of the cell body containing finely subdivided chromatic bodies, having rarely encountered a diffuse staining of this body apart from post-mortem processes.

The *nucleolus* is sometimes distinctly *swollen*, and thin sections of such nucleoli, usually discloses a reticulated structure. Some of the meshes of this reticulum may project beyond the border of the nucleolus, giving the appearance of vacuolation. In such cases the changes in the central acidophile mass of the nucleolus may be followed in sections stained by Ehrlich's tricolor mixture.

The nucleus may contain several large or small deeply

staining masses grouped about the nucleolus, and suggesting a subdivision of this body. In these granules, often called *secondary nucleoli*, the writer has been unable to demonstrate any portion of the central acidophile mass of the nucleolus, and it appears that their origin is not certainly understood.

While the above changes in the ganglion cells as demonstrated by Nissl's method are those most frequently encountered, any attempt to exhaust all the possible peculiarities of the degenerating nerve cell must necessarily be fruitless. The minute lesions appear to differ in each case and the range of minor peculiarities is practically limitless. Especially in the advanced stages of acute and chronic degeneration the aspect of the cells may be so heterogeneous that classification of lesions is impossible.

Likewise the attempt to separate the lesions of simple chromatolysis from those of true degeneration, requires, in the present state of microscopical technics, too much conjecture for the conservative investigator, especially as the physiological and pathological processes are usually blended. The early stages of the true degenerative process have not yet been satisfactorily demonstrated, and it is only when we meet with vacuolation of the cell body, with clefts, raggedness of outline, destruction of cyto-reticulum, loss of dendrites, and distinct atrophy, and when marked nuclear changes are present, that it is safe to conclude that a generally destructive process has been at work. *When acute degeneration, in a strict sense, affects the ganglion cell, its changes are usually evidenced by various forms of chromatolysis, but the true degenerative process may not and, as the writer believes, frequently does not begin until after chromatolysis is complete.*

DESCRIPTION OF PLATES.

Plate I.

Figure 1.—"Polar dendrite" of lumbar stichochrome. Specimen teased in fresh condition, fixed by heat, stained by erythrosin and methylene blue.

The chromatic bodies appear as integral parts of the reticulum, the blue fading insensibly into the red threads. The reticulated portion of the cell is sharply marked off from an envelop of granular acidophile substance which is continuous with the axis cylinder process.

Figure 2.—Normal human Purkinje cell. Specimen teased in fresh condition, fixed by heat, stained by methylene blue. The chromatic bodies are continuous with a network staining distinctly with methylene blue.

Figure 3.—Normal human archystichochrome, from motor cortex. Sat. aqueous bichloride. Methylene blue.

Figure 4.—Normal human spinal ganglion cell. Van Gehuchten's fluid. Methylene blue.

The large chromatic bodies are concentrically arranged. The achromatic substance at the pole is finely granular, and the granules are placed in indistinct radiating rows. These granules do not stain distinctly as does the reticulum of the cell body.

Plate II.—Cadaveric Changes.

Figure 1.—Medullary stichochrome of infant. Eight hours after death. Lang's fluid. Methylene blue. Very rapid and extreme vacuolation. Loss of cyto-reticulum. Coarsely granular appearance of chromatic bodies. Beginning nuclear chromatophilia.

Figure 2.—Cortical arkyochrome of rabbit, after 36 hours exposure to air. Lang's fluid. Methylene blue. Vacuolation. Coarsely granular appearance of chromatic reticulum. Complete nuclear chromatophilia. Shrinkage of dendrites.

Figure 3.—Purkinje cell of rabbit, after 48 hours exposure to air. Lang's fluid. Methylene blue. Extreme vacuolation. Growth of

putrefactive bacteria. The chromatic reticulum and bodies are reduced to a series of coarse dark granules. Complete nuclear chromatophilia. Shrinkage and destruction of dendrites.

Plate III.—Cadaveric Changes.

Figure 1.—Human Purkinje cell. Twenty-four hours after death. Lang's fluid. Methylene blue. Slight vacuolation. Coarsely granular appearance of chromatic structures. Beginning nuclear chromatophilia.

Figure 2.—Human cortical arkyochrome. Twenty-four hours after death. Lang's fluid. Methylene blue. Slight vacuolation. Partial destruction of chromatic reticulum. Beginning nuclear chromatophilia.

Figure 3.—Human cortical arkyochrome. Twelve hours after death from fracture of vertebra. Lang's fluid. Methylene blue. The chromatic reticulum is replaced by coarse granules. The nuclear membrane and network are markedly thickened.

Figure 4.—Spinal stichochrome of asphyxiated infant. Ten hours after death. Lang's fluid. Methylene blue. Rapid destruction of chromatic structures, which are reduced to coarse granules, some of which are deposited in the pericellular lymph space.

Plate IV.

Figure 1.—Large archystichochrome of motor cortex in case of sunstroke. Sat. aqueous bichloride. Methylene blue. The chromatic bodies have entirely disappeared, leaving a fine reticulum staining faintly with methylene blue. The nucleus contains several large granules, probably derived from the nucleolus.

Figure 2.—Medullary stichochrome of rabbit, killed by heating. Sat. aqueous bichloride. Methylene blue. (Section 3 μ. Zeiss $\frac{1}{12}$ apochromatic lens; artificial light; achromatic condenser; oil on condenser).

By low magnification, this cell appears uniformly homogeneous and diffusely stained. On higher magnification and special illumination, the cell is found to contain remnants of the chromatic bodies in the form of fine, pale granules. No cyto-reticulum could be discerned.

Figure 3.—Human cortical archystichochrome, in case of tetanus. Alcohol, 97 per cent. Methylene blue. The chromatic masses are almost entirely wanting, the faint chromatic network persisting. The intra-nuclear network is thickened and coarsely granular and the nucleolus presents several small clear areas.

Figure 4.—Human medullary stichochrome, in a case of sunstroke. Section 3 μ. Sat. aqueous bichloride. Methylene blue. The chromatic bodies are destroyed. The cell is largely composed of coarse pale granules, which sometimes form an indefinite chromatic network. The cell borders are rounded and the processes missing.

In sections 15 μ in thickness this cell appeared uniformly homogeneous and chromatophilic, as in the small figure.

Figure 5.—Purkinje cell in case of thrombosis of basilar artery. Lang's fluid. Methylene blue. There is uniform fading and marked diminution in size of the chromatic masses. The cyto-reticulum is very indistinct in the cell body, but a reticulum staining with methylene blue is visible in the dendrites.

Plate V.

Figure 1.—Cortical arkystichochromes compressed by distended capillary in case of acute uræmia (Case I). In both cells there is moderate perinuclear chromatolysis with preservation of reticulum.

Figure 2.—Usual changes in cortical cells in uræmia.

In the arkyochrome the network is distinct but its meshes are not always uniform in size. The nucleus contains many large pale granules replacing the intranuclear network. In the arkystichochrome there is moderate perinuclear chromatolysis and certain nuclear changes.

Plate VI.

Figure 1.—Human Purkinje cell in case of tetanus. Alcohol 97 per cent. Methylene blue. There is marked fading and partial subdivision of chromatic bodies. The reticulum of the cell body is indistinct and irregular but appears much sharper in the dendrites. The nuclear membrane is almost invisible and the intranuclear network is reduced to coarse pale granules. The nucleolus is distorted and presents the appearance of vacuoles.

This cell must be regarded as showing true degenerative changes.

Figure 2.—Medullary stichochrome adjacent to a miliary tubercle in Case I of tuberculous meningitis. Lang's fluid. Methylene blue. There is moderate subdivision of chromatic bodies especially about the nucleus. A chromatic network is visible between the bodies. The nucleus appears normal.

Figure 3.—Deep medullary stichochrome in above case of tuberculous meningitis. The chromatic bodies are entirely wanting. A faint reticulum persists, staining slightly with methylene blue. Some processes appear to have been destroyed. The nucleus is shrunken and eccentric.

Figure 4.—Axonal degeneration. Sunstroke, etc. Sat. aqueous bichloride. Methylene blue. The chromatic bodies have disappeared from the centre of the cell, leaving a chromatic network and a few fine granules. The nucleus is eccentric, but is otherwise slightly altered.

Figure 5.—Medullary stichochrome in case of acute morphine poisoning. Van Gehuchten's fluid. Methylene blue. The chromatic bodies in several parts of the cell are partly or completely destroyed leaving a faint chromatic reticulum. Some of the remaining bodies appear to have been fused together. The nucleus is shrunken and eccentric. The deeply staining rods heaped about the edge of the nucleus were abundantly present in this cell and are possibly referable to the shrinkage of the nucleus.

Figure 6.—Purkinje cell in case of eclampsia. Lang's fluid. Methylene blue. The chromatic bodies are much faded and partly subdivided. A chromatic reticulum is visible. The nucleolus is enormously swollen, the nucleus is small and markedly chromatophilic.

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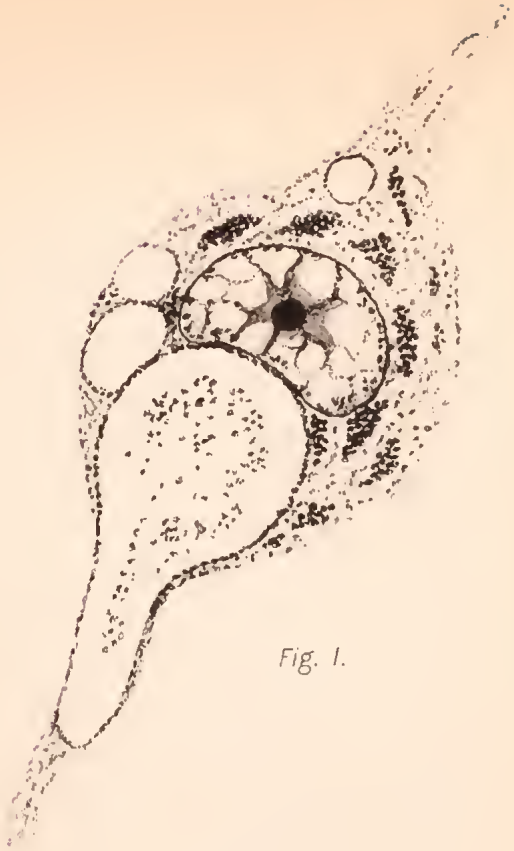
Fig. 2.

Fig. 3.

Fig. 4.



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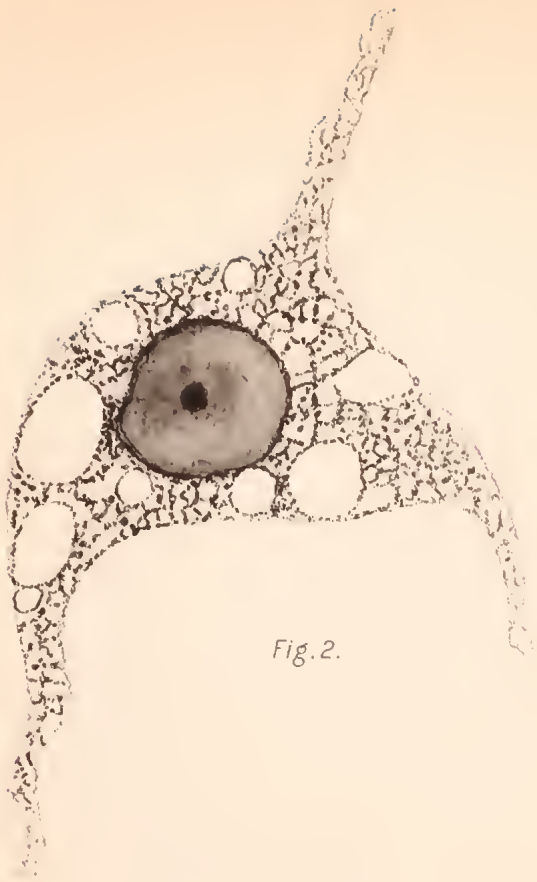

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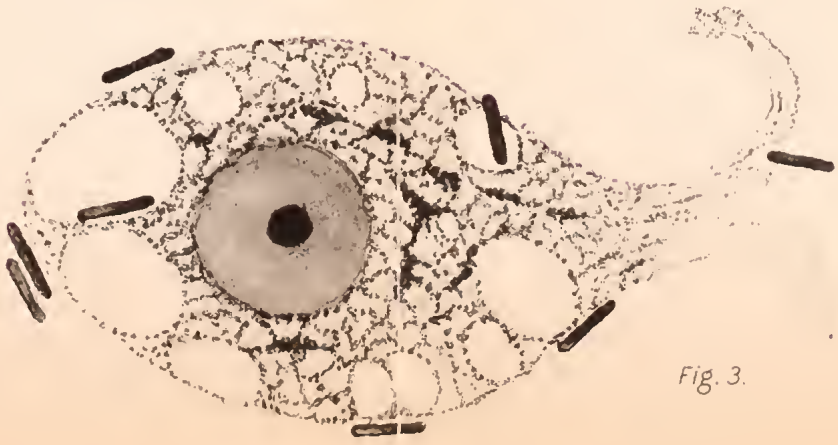

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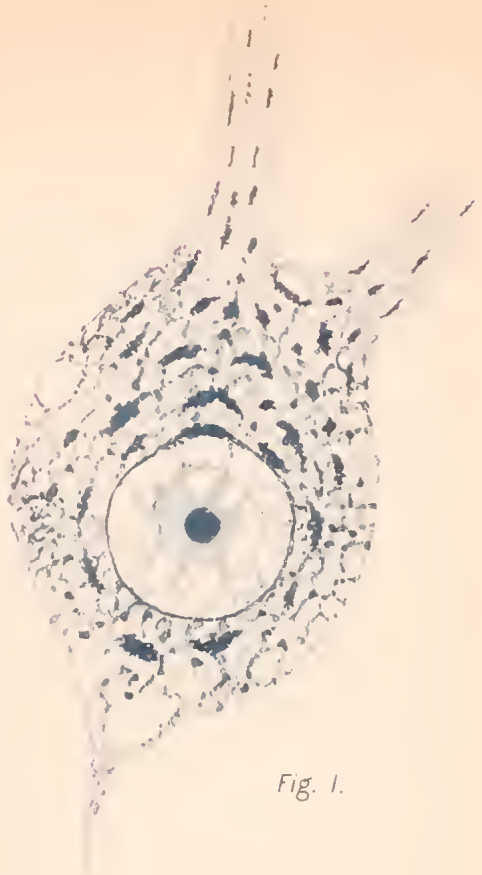

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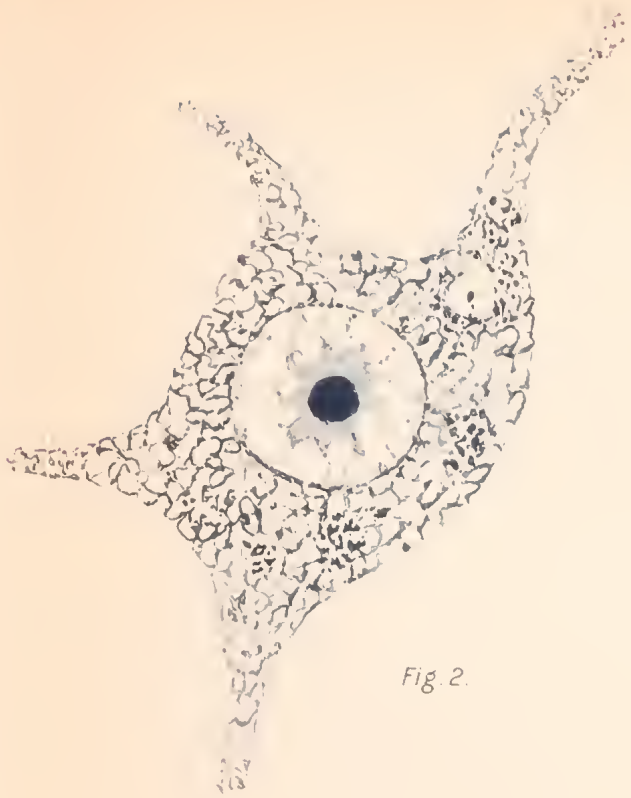

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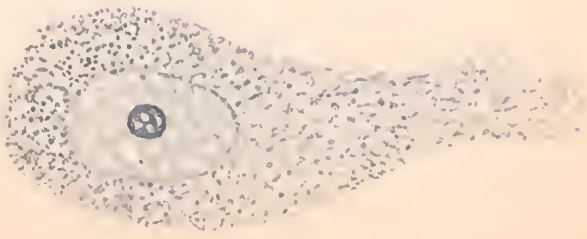

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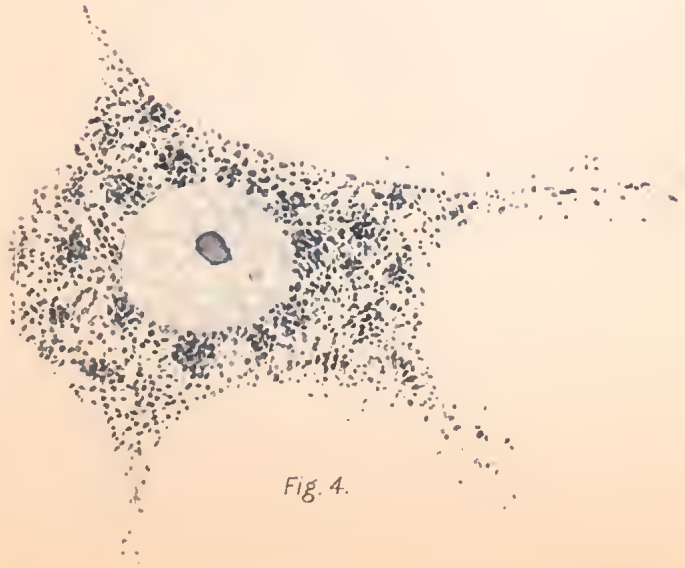

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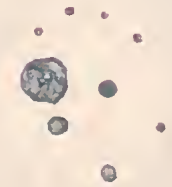

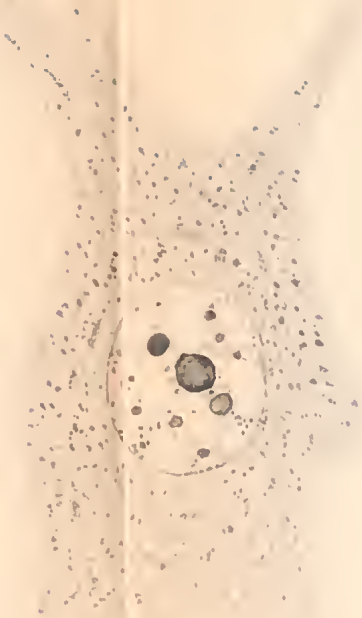

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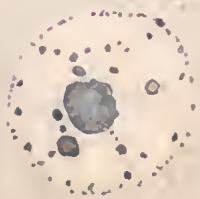

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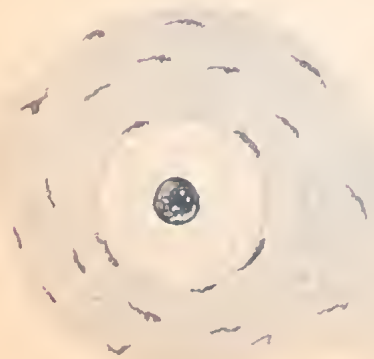

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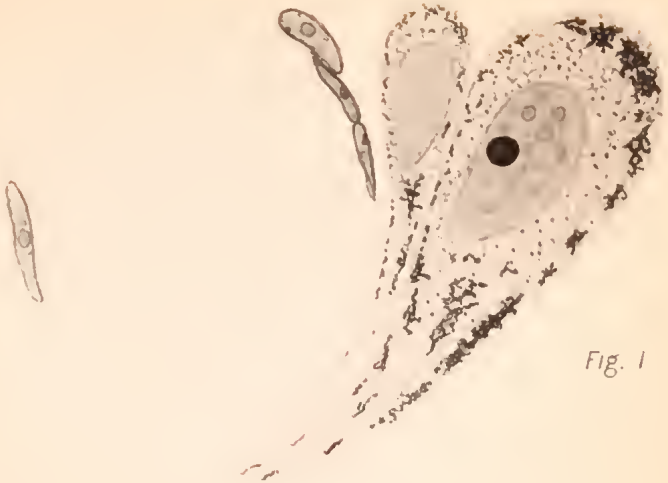

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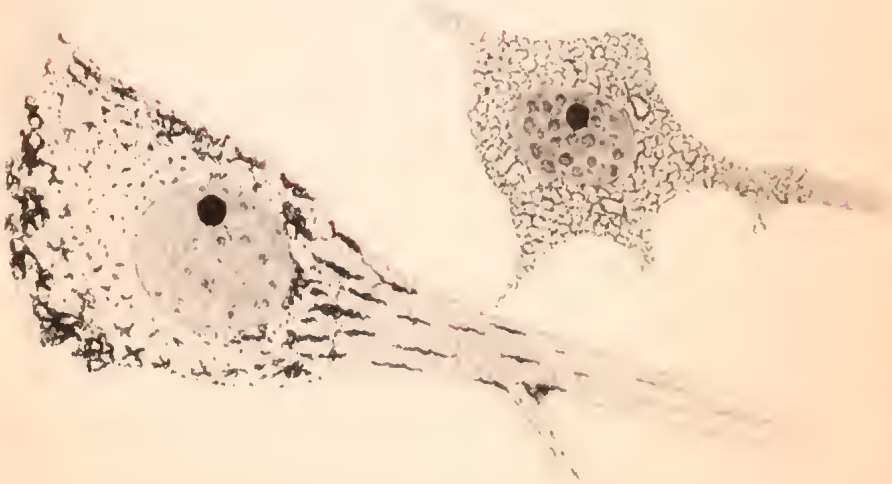

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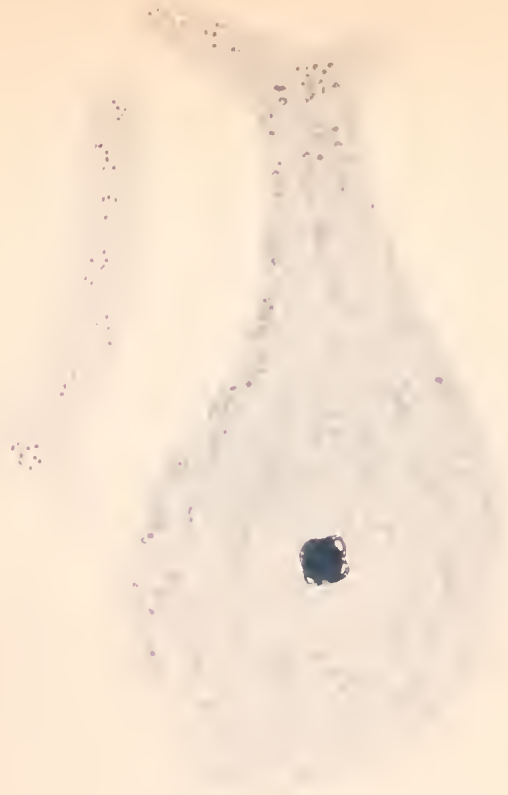

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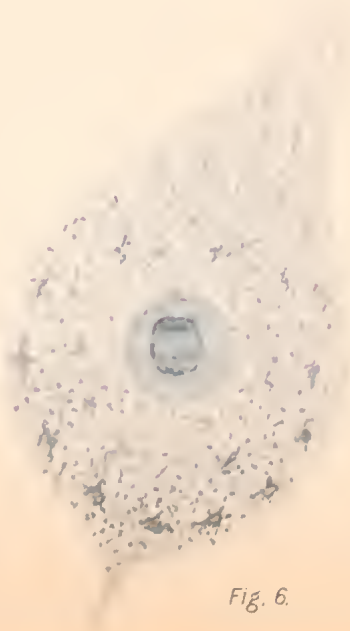

Fig. 6.

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BIBLIOGRAPHICAL CONTRIBUTION TO THE CYTOLOGY OF THE NERVE CELL.

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The present contribution is an endeavor to give the titles of the most important contributions to the cytology of the normal and diseased nerve cell. The greater number of these cited observations were studies in which the Nissl method, or its modifications, was used; so that in one sense this may be called a "Nissl Bibliography," but observations made by other cytological methods are also included. Naturally the work along the lines laid down by Golgi, and Ehrlich, in his *intra vitem* method, has not been included.

It is not improbable that a number of important articles have been omitted from this list, though the compiler has tried to make it as complete as possible. I am indebted to Dr. James Ewing and Mr. O. Hensel for assistance in the preparation of this bibliography.

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NEUROLOGY AND PSYCHOPATHOLOGY

PRELIMINARY EXPERIMENTAL STUDIES IN A CASE OF AMNESIA WITH A DISCUSSION OF THEIR PSYCHOPATHOLOGICAL SIGNIFICANCE.

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Binghamton, N. Y.

The following case, although for some time resident in the hospital, has only recently come under my personal observation. As soon as I had recognized its importance I communicated with the Pathological Institute of the New York State Hospitals and the experiments described in the succeeding pages were undertaken under its direction and with its co-operation. Dr. Boris Sidis, the Associate in Psychology and Psychopathology, with whom my correspondence was conducted, finally suggested that it would be well to report the results so far attained and in accordance with this suggestion I present the following article:

Cases of amnesia have of late attracted considerable attention and assumed a position of importance among the

disorders of the mind. It is not at all uncommon to read of some person who has, from one cause or another, lost his personal identity, and it is fair to presume that a certain number of "mysterious disappearances" reported each year are cases of this character.

It is only necessary to call attention to this class of cases to see at once of what importance they are both from therapeutic and medico-legal aspects. With a lively appreciation of this importance and a belief that any light, however dim, which may be thrown on this condition will be welcomed, I offer the following study, incomplete as it is, only hoping that I may add what is lacking at a future date.

On the fourth day of February, 1897, a patient was admitted to the Binghamton State Hospital under the name of John W. He was brought from the D. county jail at D. where he had been sentenced to sixty days for failure to pay a board bill. Shortly after his confinement it was noticed that his mind was defective and his memory poor. He was not certain of his own name and could give no rational account of himself, where he came from or what he was doing in D. An examination of his mental condition was therefore made and resulted in his commitment as insane.

His commitment papers state absolutely nothing about his past life. They merely state that he was despondent, sat with lowered head talking to himself and complaining that the boys threw sticks at him and the slivers stuck in his head. He also said that someone was squirting water at him and talking to him at night and was on guard constantly to keep them from hurting him. The medical certificate goes on to state that he knew nothing of his past life and, although he tried, was unable to recall anything about it.

At the time of his admission, his condition bore out the statements occurring in his commitment papers as above. In addition, however, he said he belonged to the 28th Regiment and that at one time while standing on a bridge had been struck on the head by something hard and knocked in the water.

His history for the first few days after admission was uneventful. He was somewhat mentally confused and dull at first, but progressively brightened up. On the 27th of February a note occurs in his case in which it is stated that a few days before, while watching a card game, the names of the cards came to his mind and on joining in the play it was found he understood the game thoroughly. In the same manner he recalled the method of doing certain sleight-of-hand tricks which he witnessed at an entertainment given for the patients by a prestidigitateur. His duplication of the tricks was done with such finish as to lead to the conviction that he had at one time been a professional.

Incomplete and isolated recollections of his former life now kept coming to him and he immediately recorded them in writing, hoping in time to be able to establish his identity in this way.

The next note of importance in his case occurs under date of May 25, 1897, and describes the following occurrence without, however, referring it to a definite date:

While looking at a tobacco box, he saw the name of the town of M. in Germany and it immediately flashed upon him that he was born fifteen miles from there. An atlas being procured and the names of the towns in the immediate vicinity read to him, he recognized A. as the place of his birth. This discovery deeply affected him so that he suffered from insomnia that night and even had to take a hypnotic the following night.

Mr. W. is a man of about sixty-five years of age. He speaks English well but with a pronounced German accent. For many months he has been one of our most trusty patients, having parole of the grounds and being at times permitted to go to the city unaccompanied. He has worked for a long time in the drug store and proved himself to be thoroughly reliable. His general health is not first-rate. He suffers especially from very severe headaches which sometimes last several days. He presents well marked arcus senilis and degenerated arteries. Mentally he is quite emotional, especially when speaking of his past life, and on these occasions I have often seen him on the verge of tears. His memory for recent events is ordinarily good, except when suffering from headache, when he complains of a feeling of mental confusion and an inability to remember things for which he is sent on errands.

Glimpses of his former life keep recurring to him from time to time, and he has faithfully recorded them, until now he has collected quite a number of isolated, disconnected and fragmentary events of the past. To illustrate fully the character of these recollections and the way in which they have occurred to and been recorded by him, I here insert a full and complete account of his past life, so far as he was able to recall it, which I requested him to prepare for me in writing:

"Recollections as coming to me at times and write them down at once, at night in bed and sometimes in daytime and marked down at the moment or would be lost again in an old cover of a book, I find that I belong to the 28th N. Y. Militia of Brooklyn, by reading the history of the Rebellion between the North and South. Many circumstances come back to me by reading and dreaming at night. On the way from Washington to New York,

according as it came to me, that I was riding on top of a car and was struck by a bridge in the head. Many circumstances in a note-book, the writing with a pencil and some of the leaves lost, I cannot recall them at the present. I remember the picture of Abraham Lincoln and General Scott, remember standing by General Scott, holding his horse on the night after the battle of Bull Run above Washington on Arlington Heights. I remember talking in German and could not understand English, being on picket, firing in the air and we formed a square in an open field. It came back to me one night that I never received any pay, a young man in my camp made me sign a paper and then took me across a river in a big boat. Remember couldn't hardly speak English, was wounded, took me to a farm house, remember they spoke and dressed different from anybody else, called me the 'crazy Dutchman.'

Suffered a great deal with headache, suffering which I cannot explain, not near as bad as I had them. I cannot remember where I came from. There is times now when I am sent on an errand I cannot remember it, and at times when I have the headache I have to mark everything down or it is gone. I am doing some sleight-of-hand work, cannot say that I ever done any before or not, it came back to me here at the hospital, where I have seen a man perform, that I must have done that before or picked up from him, but I have done things some different from what he has done. I am living in hopes that I am improving through the instrumentality of Dr. White, I have faith in it. I cannot remember all by his experiments with me, he is writing it down and he will give to me when I want it. I have all the doctors names which I put in my book and the nurses' names on the ward. When I have the pain in the head I cannot remember anything. Very often nights I hear knocking at the door when I wake up and look, nothing and nobody there. I can call to memory 8th N. Y. Regiment, Garibaldi Guard, 45th Pennsylvania, Schwarze Jager, Buck Tail Rifles. The colonel who commanded the 28th, cannot recall his name

till I look it up, but I can picture him to me, a short heavy man, he was Lieut. Colonel in command. I am not sure that he or the Colonel had a merchant tailor establishment. I remember and can describe the following generals: Fremont, Blenker, McDowell, Stahl, Shields, and also places where I been which I can describe, Harper's Ferry, Winchester, Charlestown, Middletown, White Post, Mount Jackson, Strasburg, Harrisburg, Edenburg. It comes to my memory that I was wounded near Fort Republic but I am not sure of it."*

It is noteworthy that these flashes of the past are more prone to occur after he has retired for the night. When this happens he has been in the habit of springing out of bed for the purpose of recording them. Even with this promptitude of action on his part he often fails to secure a record as the recollection vanishes before he can transfer it to paper. This forgetfulness is characteristic of all the recollections which have come to him. He can tell very few of them without referring to his notes, unless they have for some reason been frequently and forcibly presented to him.

At the time of his examination Mr. W. was somewhat despondent and appeared to those about him to be talking at random. When admitted and for a few days thereafter he was confused and somewhat dull, but immediately began to adjust himself to his new surroundings and shortly his mental condition began to improve in every respect save one—his past was an absolute blank. His entire life previous to his admission was completely effaced from his memory so that he did not even know what his own name was. He had been committed as John W., but he had absolutely no knowledge whether

* The more or less disjointed and ungrammatical way in which the account is written is dependent in part upon the fact that the patient has never written much in English although he speaks it quite well.

that name was his name or a name given him in default of his own.

Here then, we have a case of amnesia. A man whose past is as completely blotted out from him as if it had never had any existence. Is his past forever lost or is it possible that at some future time the memories of his former life may return? In other words, has he suffered from an organic cerebral affection resulting in the actual destruction of nerve elements thereby placing an impassable gulf between the present and past, or have these memories dropped out of consciousness as a result of the suppressed functional activities of certain brain areas?

Certain facts in the case lead us to the conclusion that the second one of these hypotheses is the correct one; namely:—those evanescent flashes of a past which from time to time have obtruded themselves into the patient's consciousness only to disappear as rapidly as they came, leaving scarcely a trace behind them. The occurrence of these states leads us to the conclusion that the memory pictures of many years have not been ruthlessly wiped out, but that they still exist in that great unexplored region of the subconscious, buried deep beneath the threshold of his personal consciousness, and separated from it by a gulf which no effort of his can avail to bridge.

Deeply buried as the memories of his past may be, in the depths of the subconscious, still they have given ample evidence of their existence, especially, by their recurrence in the form of dreams. Fragmentary and fitful as have been these evidences, still they have been sufficient to suggest that possibly some method of experimentation might serve to lay bare more completely the regions of the mind in which they reside. The results of such experiments would enable us to differentiate with certainty between the

two possibilities of organic or functional disease. For such a method we are indebted to Dr. Boris Sidis. It is known as the method of hypnoidization, and he describes it as follows:* "This method consists in the following procedure: The patient is asked to close his eyes and keep as quiet as possible, without, however, making any special effort to put himself in such a state. He is then asked to attend to some stimulus, such as reading or singing. When the reading is over, the patient, with his eyes still shut, is asked to repeat it, and tell what came into his mind during the reading, during the repetition, or after it. Sometimes, as when the song stimulus is used, the patient is simply asked to tell the nature of ideas and images that entered into his mind at that time or soon after." By this method we are enabled to distract, draw off, completely occupy, in fact remove, as it were, the personal consciousness of the patient and thus allow the subconsciousness to act unhampered by the inhibitions of the upper self. The personal or upper consciousness of the patient being fully occupied, by close attention to the stimuli used, fails for the nonce to exercise its inhibitory control over the subconsciousness which in its turn, finding itself thus relieved from censorship, acts spontaneously.

The stimulus used in this case was the music-stimulus, a combination of both vocal and instrumental music.

On Nov. 15th, 1898, the following ideas and images came to the patient's mind under the influence of this stimulus:†

Riding on a steamboat.

Saw an old doctor with gray hair and beard. A young man came to him after he was hurt in the army and took him to New York.

* Dr. Boris Sidis—The Psychology of Suggestion, p. 224.
† Each paragraph gives the results of a separate experiment.

An accident on the Ohio river between two steamboats occurred near Madison and over one hundred lives were lost. The names of the steamboats were "United States" and "America." He could see fire and hear the shrieks of the injured very plainly.

All these ideas occurred to him very vividly. He could almost see the occurrences described and by immediate questioning I could bring out facts additional to those which he had told me spontaneously.

On Nov. 18th, 1898, the experiments were continued under the same conditions, with the following results:

Sick in bed. He saw two doctors, one named Hunter. There were a lot of persons about.

After this experiment he turned to me and asked me if I had touched him on the head. I replied in the negative, but had to reassure him as he was quite incredulous, the sensation had been so plain. It had come to his mind that someone had struck him on the head and that he was picked up; there was a large crowd about and it was night-time. This experiment illustrates well the vividness with which these subconscious states are endowed.

Hypnoidization was now resumed.

He thought he was buying horses with a man, either in Philadelphia or New York.

He saw a covered wagon come to pick him up and the old doctor was there. He heard them cry out "corner of Lake and Fifth Ave." He was placed in the wagon.

Next thought himself in New York crossing the river. A young man sent him off somewhere.

He was taken to a hospital—the Presbyterian.

In Virginia, with the Quakers, who called him the "Crazy Dutchman." They used "thee" and "thou" in talking. He says he could not answer them well.

The patient now requested to be allowed to rest until some other time as he was suffering from a severe headache which he said started with the idea of the blow on the head which he had during hypnoidization and which is described above. He says further, he did not have any headache before this idea came to him.

On Nov. 22d again these experiments were continued with the music-stimulus. The results were as follows:

Thought he was marching with the army, forty-five men were lost by the sinking of a boat in the middle of the river. These men, he thinks, belonged to the 45th Pennsylvania regiment.

Marching in Grand and Greenwich streets. Crossing river to Hoboken. Quartered in big brick house.

While I was away for a short time and the music still continued, he closed his eyes and listened as he had been doing, and it came to his mind that he had boarded at one time in a house located at Seventh avenue and avenue A. He also thought of being eighty days in a sailing vessel; also of selling horses in Twenty-third street. It also came to his mind that he was put on a car and taken to a large house with a big round top with a figure on it.

He now opened his eyes with a sudden start and the exclamation, "they got it." In answer to questions he said he was robbed but did not know by whom.

On shutting his eyes again it came to him that when he was robbed he lost a diamond ring of 1⅛ karats, a watch and some money.

At the end of these experiments he called me aside after we had started out of the room and said that Rau was the name of the person who kept the boarding house, the location of which he had, however, already forgotten.

These experiments as recorded, are the results given by

the method of hypnoidization. They are recorded in the same disconnected order in which they occurred, relating to fragments of a past, often separated, in all probability, by many years. They show that the patient's subconsciousness really possesses memories of his past life, and when relieved of the inhibitory action of the upper self is able to express them, albeit, in this disjointed manner.

The mental state of a patient during hypnoidization has been termed by Dr. Sidis the hypnoidal state, and should be clearly distinguished from the hypnotic condition with which it has practically nothing in common. During hypnosis, the personal consciousness is completely dissociated from the subconsciousness which in its activities manifests a remarkable susceptibility to suggestion. During the hypnoidal state, on the contrary, the personal consciousness is merely distracted by being occupied with stimuli, and the subconscious only wells up to the surface here and there in an entirely irrelevant manner. The phenomena of suggestibility are not present and the subconscious lapses into the depths from whence it arose immediately the stimuli are removed.

The disconnected, haphazard way in which these subconscious memories recurred in the experiments recorded indicate that it would be impossible ever, by the methods therein employed, to construct a coherent, connected history of the patient's past. For the purpose of determining the experimental possibilities in this direction, however, without the employment of hypnosis, against which the patient was strongly predjudiced, I arranged some further experiments. My idea in these experiments was to endeavor to more completely distract and occupy with stimuli, the personal consciousness of the patient and by so doing, uncover the subconsciousness more than had

been done before. I hoped that I might thus be able to bring myself into relation with the subconsciousness and possibly direct its activities.

This end I hoped to achieve by applying stimuli to more than one sense and also by increasing their volume so as to more completely occupy the upper consciousness and distract it from its inhibitory control of the lower. With these ideas in view, I performed the following experiments:

Mr. W. was placed in a reclining position. He was given the electrodes of a Faradic battery and told to listen to the buzzing of the machine. I then determined by experiment the amount of current he could take just short of producing pain. I now told him that as the ideas came to his mind he was to speak them out without waiting until I asked him to. He now closed his eyes and I adjusted the current to the amount determined as above. He began to tell me the ideas as they came to his mind. I immediately began to converse with him, asking him many questions which he answered quite readily. In this way he told me he was in Virginia with the army marching. He was near Harrisburg marching to Luray and Fort Republic. Gen. Ashley was killed by the Buck-tail Rifles. He put up in camp for the night. In the morning after bugle call the sergeant called the roll. He told me that the sergeant called his name as Dave S. The Faradic current was now turned off and the upper consciousness immediately resumed its sway. When asked what he remembered, he said he remembered being in Virginia marching along; also remembered the Buck-tail Rifles. He had no recollection whatever of my having spoken to him. He seemed to recognize the name of Dave, when spoken to him and said the name S. sounded like his name; the "S" was right but the rest was not quite like it.

Mr. W. was now placed in position for another experiment in the same way as before. The Faradic current was adjusted in the same way and he was directed to close his eyes and listen to the buzzing. He now told me that he was in Wheeling, Va., in a hotel near the river tending bar. I now asked him point blank what his name was. He replied "Adolphus S." In reply to questions regarding the name "Dave" which he gave me in the last experiment, he said he had a brother Dave who was now dead. He also said he had two sisters, Bertha and Lizzie. There were several others in the family but he did not seem to be able to recall their names. He said he was not married. The Faradic current was now stopped. He was spoken to but did not reply. It was necessary to tap loudly on the table, when he opened his eyes with a start. When asked what he remembered, he said he recalled being in Virginia. He was asked the name of his brother and himself. He replied that it seemed as if he had known them a few moments ago but could not now bring them to mind. When I spoke the names to him and also the names of his sisters, he said they sounded familiar. Adolphus S. sounded much more familiar to him than John W., and when I asked him to write it both in English and German, he said it looked familiar to him. In addition to recognizing the familiarity of the names of his family, he said there were many more of them whose names he could not recall.

The ends which I had hoped to achieve by these experiments were attained, though possibly not as completely as I might have desired. The experiments were discontinued, however, because the patient invariably complained of very severe headache following them. The mental condition induced by these methods must again be

distinguished from the hypnotic state. This distinction is shown especially in two particulars, viz., the absence of suggestibility and the spontaneity with which the personal consciousness resumed its sway. When he was under the influence of the stimuli I suggested to him on one occasion that the severe headache from which he was suffering at the time would immediately improve and that he would feel much better at the completion of the experiment. This suggestion produced absolutely no effect. It will be noticed that in the first experiment the upper consciousness asserted itself at once, merely by the withdrawal of the stimuli, while in the second experiment it was only necessary to tap on the table to produce the same effect; this would never have occurred, except by suggestion, if the state had been one of hypnosis.

In our old conception of the nervous system with the brain cells in anatomical continuity one with another, it would be difficult indeed to explain how such a condition was possible. It would be necessary to postulate the suppression of nerve currents along certain tracts which, however, offered no obstruction to their flow, and it would be difficult to offer a cogent reason for the persistent avoidance by these currents of pathways of discharge which were always open.

The advent of the theory of the anatomical unity of the neuron, has however, precluded the necessity of finding an explanation under these disadvantageous circumstances.

Each neuron, that is, the nerve cell and its processes, is anatomically distinct and separate one from another. Such connection as subsists between them is purely a physiological and not an anatomical one. The terminal ramifications of the processes of the several neurons are intimately related to each other, but there is reason to

believe that actual contact does not occur. When the distance between two neurons is sufficiently minute it can be bridged by the nerve force, in a manner similar to that in which the space between the knobs of a Holtz machine is traveled by the electric spark when they are brought near enough together. This bridging of the intervening space between neurons brings them into physiological association. When, however, the distance between two neurons becomes too great to be bridged by the nerve force, they cease to maintain physiological relationship. This condition may be brought about as the result of any cause which produces a contraction of the neuron terminals.

It can be readily appreciated how, in accordance with this explanation, not only one neuron, but many neurons, in fact, whole groups of physiologically associated nerve cells may thus, by the widening of the space which separates them from their neighbors, become dissociated in a group from them and thus produce, concomitantly, a dissociated conscious state.

Dr. Sidis, in his work before quoted, has shown how the application of this theory may explain amnesia or, in fact, all of that great class of cases in which consciousness becomes disaggregated or split up into parts, mental states resulting from this disaggregation which are dissociated from the personal consciousness and exist entirely apart from and unknown to it. I refer especially to that ever increasing category of "manias" and "phobias," the so-called obsessions, imperative concepts and morbid impulses, together with hypnotic and post-hypnotic, somnambulic and hypnagogic states, and some of the insanities, especially those involving personality metamorphosis, such as paranoia. In all these cases we see the results of

ideas and impulses which have their origin and seat in the subconscious. In many instances, especially in post-hypnotic and psychopathic states, the upper consciousness appreciates the absurdity or impropriety of the ideas and impulses, which continually assert themselves and endeavors to control their manifestations. Lying as they do, however, beyond the operation of the patient's will power, they continue with unabated force to obtrude themselves into his personal consciousness. Here, indeed, we have a fruitful field for study but one which the limits of my paper forbid me from further discussing.*

In order more fully to appreciate how this state of affairs may be brought about, let us pause at this point and consider the constitution of consciousness.

Following Dr. Sidis again we may say that the content of consciousness may be divided into units which we will call "moments-content" † and that a synthesis of a number of these moments-content constitutes the unit of consciousness: the moment-consciousness.

‡ "We must discriminate between the psychic content that may be characterized as the moment-content of consciousness and the synthesis of that content. It is this synthesis of the content that constitutes the nature of a moment-consciousness. In short, a moment-consciousness is content *plus* synthesis."

Now these units of content and of consciousness corre-

* Ibid., p. 269.

† Moment as here used must not be understood as referring to extension in time. "While in the schema of objective time the present moments are in a continuous flux, the present moments of consciousness are far from being in a parallel incessant change. The moments in the schema of time may go on flowing, but the present moment of consciousness may still remain unchanged; nay, it is even fully conceivable that a present moment of consciousness should fill a whole eternity. The radical difference of those two moments is well illustrated in the popular story of the monk, who happened to listen to the song of a bird from paradise for but a single moment and found that meanwhile a thousand years had passed away."--Sidis, Psychology of Attention, p. 196.

‡ Ibid., p. 203.

spond to the simplest groups of nerve cells and as they are synthetized into more and more complex groups until we reach the highest manifestations of conscious activity in the normal mind, it is fair to presume that this synthesis is represented in the nervous substratum of mind by a corresponding synthesis of groups of nerve cells by means of associations of ever increasing complexity.

The application of this theory to the case in hand is evident. Our patient at some time has received a shock so severe that as the channels of conduction in the brain were flooded with the resulting stimulus; a stimulus inimical to the integrity of the nerve cells and threatening their destruction; groups of these cells have retracted their delicate end arborizations and severed their connections with those about them. This retraction takes place under conditions which closely remind us of the retraction of the pseudopodia of an amœba on the advent of a noxious stimulus.*

The mental condition resulting from this solution of functional continuity between groups of nerve cells is a dissociated state of consciousness. The associated moments-consciousness, represented by the assemblage of cells which have retracted from their neighbors, thus fall out of relation with the patient's personal consciousness and drop into the region of the subconscious.

Here we have a vindication of our methods of diagnosis and an explanation of their significance. If the shock which produces a dissociated conscious state is actually destructive in its effects so that the nerve cells are actually destroyed the moments-consciousness which they represented will be forever removed from the

* Ibid., p. 213.

possibility of synthesis, in fact, will cease to exist. If, however, the shock stops short of destruction in its effects only producing a functional disaggregation of nerve elements then the moments-consciousness represented by the disaggregated elements will still exist but in a dissociated conscious state, out of relation to the personal consciousness, *i. e.*, in the subconscious.*

In the case in hand, we have a combination of these two conditions. It is true that we have been enabled by our methods of experimentation to uncover memories which existed in the subconsciousness of the patient of which he had no knowledge. The significant facts, however, remain: That these memories have at best been but fragmentary, disconnected, and uncertain, and further, the patient has been unable to synthetize them in his upper consciousness. They are forgotten immediately they are recalled and lapse again into the subconscious. In other words, along with a well marked dissociation of consciousness of a functional or psychopathic nature, there goes hand in hand a neuropathic element corresponding to actual neuron degeneration. How much of this latter element may have been due to the original injury and how much may be the result of subsequent senile changes, it is impossible to state, but its occurrence makes the prognosis very unfavorable and emphasizes well the importance of an accurate diagnosis in these cases.†

By our method of hypnoidization we have been able to so thoroughly occupy the personal consciousness with stimuli as to remove its inhibitory control from the sub-

* Ibid., p. 231.

† For a definition and discussion of psychopathies and neuropathies, see article "Neuron Energy," by Van Gieson and Sidis, ARCHIVES OF NEUROLOGY AND PSYCHOPATHOLOGY, Vol. I. No. 1, 1898.

conscious, thus allowing memories to emerge from depths where they had been long buried.

At this point it is natural to ask the question, If a dissociated conscious state is due to the severance of functional relations of association between certain groups of cells, why, when the cause of this disaggregation ceases to act, are the associations not reformed ?

The answer to this question lies in the fact that the neuron has suffered from the shock to which it was subjected a loss of energy which makes it impossible for it to resume its normal functional activity, immediately the cause of its retraction is removed, until that energy is renewed.

In the same way that we have before considered the neuron as an anatomical unit we must now consider it as a physiological unit. Each neuron must be considered as possessing a certain amount of energy which manifests itself in functional activity. In our case the shock which caused the amnesia has drafted the energy of the disaggregated cells so far beyond the normal point that, unable to recuperate, they fail to resume their normal functional activities and place the moments-consciousness which they represent, in relation with the personal, or upper consciousness of the patient.* One of the directions in which this functional activity is manifested is toward keeping up relations with the neurons in the neighborhood. Whenever the neuron energy is by any cause lessened in amount then this relationship becomes more difficult and finally impossible to maintain. Thus we see that causes which tend to bring about this disaggregation of neurons by lessening their energy and thus causing

*For a discussion of the subject of the energy of the neuron see article, "Neuron Energy," by Van Gieson and Sidis, ARCHIVES OF NEUROLOGY AND PSYCHOPATHOLOGY, Vol. I, No. 1, 1898.

contraction of their terminals, must concomitantly tend to cause dissociated states of consciousness.

In the foregoing pages I have discussed the subject of amnesia from the standpoint of the particular case presented for consideration, dwelling on the general psychopathology of amnesia and the methods of diagnosis.

In a later number of the ARCHIVES, it is hoped to publish a further account of the case with the results of more detailed experimentation into the special psychopathology of the condition as manifested in this patient.

Since the preceding article went to press I have had my attention called to the possibility that some persons might seek in simulation an explanation of some of the phenomena described therein. In this connection I would state that Mr. W. has now been in the hospital for upwards of two years. During this period he has been under continuous observation and for the past few months his work in the drug department has brought him into very frequent contact with the several medical officers and the pharmacist. The uniform impression which he has created upon all is that of a thoroughly reliable, honest old gentleman whose chief aim in life is to recover the memories of his past. Even now in describing his condition I have often seen his eyes fill with tears and upon one occasion at least I remember that he quite lost his self-control and wept. I have seen many malingerers but none who have succeeded in playing a part for anywhere near as long as two years without exciting suspicion.

For some weeks past Mr. W. has been failing both physically and mentally. Senile changes are creeping on apace. Even if it were admitted, for the sake of argument, that he might have been able to carry himself constantly in a false attitude for months, yet surely, now, when his mind is giving way to the decay of old age it must break down under the strain. This, however, has not been the case; on the contrary, Mr. W. impresses me to-day, after an intimate acquaintance of months, as being the very personification of honesty.

Further, I would state that my experiments were conducted without first discussing with the patient the results I expected to obtain. In fact, I make a routine practice of avoiding this in all my cases. I may add, that, in any case, I do not consider Mr. W. of a sufficiently high grade of mentality to carry out a scheme of simulation involving symptoms such as he presents.

ACROMEGALIA.

HARLOW BROOKS, M. D.,

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INTRODUCTION.

In the *New York Medical Journal* of March 27th, 1897, the author published an abstract report of a case of acromegalia with autopsy. Since this time, the writer has been able to secure, through the generosity of Dr. Fraenkel, an autopsy on still another instance of the disease. The tissues from the two cases have been thoroughly studied microscopically and it seems to the author that the findings justify the following detailed report. In addition to the tissues from these cases, portions, notably the enlarged pituitary bodies, from other acromegalics have been examined. While they tend to support the theory of pathogenesis indicated by the following two cases, it is unwise, for obvious reasons, to include these brief and incomplete observations in the final study of the disease which concludes this paper.

The bibliography of acromegalia, which is found at the end of this article, was prepared by Miss Amalie Busck, Librarian of the State Pathological Institute, who has rendered the author much valuable assistance in collecting and translating the literature, extending up to the present date, which has appeared on the subject.

For the first case, already mentioned as abstracted in the *New York Medical Journal*, the author is indebted to his chief, Dr. E. K. Dunham, Director of Carnegie Laboratory, who, through his characteristic kindness, permitted the writer to study and report the case.

This paper was given to the editors on June 1st, 1898. While it was awaiting publication an acromegalic who had long been under observation at the Montefiore Home, died. The case is of peculiar interest as it represents the terminal stages of the process, and as it has been carefully observed, the author deems it wise to insert it as case III in this article.

Chapter I.

CASE I.—HISTORY.

The patient was admitted to the J. Hood Wright Memorial Hospital, December 2, 1896, having been brought in by the ambulance, while in a semi-comatose condition.

From the history kindly furnished by the house staff the following abstract has been made:

Dr. Baruch, Visiting Physician;
Dr. LeWald, House Physician.

Patient, A. S., a man aged thirty years, of English birth and parentage. He has habitually indulged in alcoholic beverages in moderate amounts. He seems to have been in excellent health up to 1891, when he received a severe fall which resulted in a scalp wound; the patient's brother, an unusually intelligent man, noticed no change in his condition following this injury. In 1893 the patient was still in good health. At this time he weighed about a hundred and seventy-five pounds, wore a No. 7 hat, 7½ glove, and 7½ shoe. Three years later he was obliged to wear an 8½ hat, a No. 11 shoe, and his hands became so large that it was necessary to have his gloves made to order. Meanwhile the weight had increased to two hundred and fifty pounds. During this time, while in Chicago, he had been treated for acromegalia, and after some treatment the progress of the disease was thought to have been arrested.

About six months before the patient entered the hospital he was thought to have syphilis of recent origin, and received treatment for the same, with abatement of those symptoms. For the last two months he had considerable trouble with the right eye, and was treated, apparently without any result, for syphilitic iritis. He was at this time suspected of using narcotics, but no direct evidence on this point can be found, the supposition apparently resting only on the alternating irritable and drowsy condition of the patient, and on the symptom of great thirst. His appetite finally became very poor, although the great thirst still persisted.

His mental condition, manifested by drowsiness and irritability, constantly became worse, and at times he was irrational. He had attacks of dyspnœa, some of which were of long duration. He constantly complained of intense thirst.

After a short walk one day the patient went into a state of collapse, and the next morning when seen by the ambulance surgeon he was still in a stuporous condition, yet able to answer questions, when aroused. The tongue was coated and dry. The skin somewhat cyanotic. The pulse was full, but feeble and rapid. The temperature 92.2°. The abdomen was distended and tympanitic. The right pupil was normal in size and action. The breath had a peculiar sweetish odor.

The urine, which was drawn by the catheter, was found to contain two per cent of albumen and 7.5 per cent of sugar. His condition of stupor gradually deepened, and the next morning he died. Just before death the temperature, which had gradually risen since his admission, stood at 103.8°; pulse, rapid and feeble, 128; respiration, 38.

After the writer's preliminary report had been published, he was enabled through the kindness of the patient's brother, to obtain some very important data bearing on the history of the case.

The patient was a man of more than ordinary attainments, and within three days of his admittance to the hospital was in charge of a large business enterprise. He

was a man of considerable mechanical ingenuity and ability, having done some very excellent work in electro-mechanics and in photography. The nature of his work was such as to demand close application and the constant employment of a considerable knowledge of mechanics.

His business activity apparently suffered very little from the disease, and, notwithstanding his drowsy condition during the last few weeks of life, his work remained in every way satisfactory up to within four days of his death, when he found himself too weak to continue it. After death his books and papers were found to be in perfect order.

Muscular weakness was quite actively progressive for some time previous to his admittance to the hospital.

In 1893, when he left home, he was a handsome and powerful man. On his return three years later, he had so changed that his relatives did not recognize him and his appearance, as compared with a photograph taken before 1893, was most strikingly characteristic of acromegalia. The patient never complained of suffering from headache or from other pain of any considerable degree.

The unfortunate death of Doctor Swinburne, who treated the patient's eyes, has rendered it impossible to obtain an account of the ophthalmic history and examination.

Bedside Chart.

Temperature, 99.2°; pulse, 120: respiration, 30.

Urine.—Straw color, clear, acid, sp. gravity 1.023; albumin, 2 per cent; sugar, 7¼ per cent.

Treatment.—Put to bed; milk diet; ℞ Magendie M vii at 11.30 A. M. hypo.

2.15 P. M.—Catherized and urine oz. xxxiii obtained; Ex. as above.

2.45 P. M.—Is in a marked stupor; given castor oil oz. ii and water oz. iv.

4.00 P. M.—Temperature, 101°; pulse, 132; respiration, 26; is restless and shouting out; given Magendie M. vii ss. hypo.

6.30 P. M.—Urine oz. v by catheter.

8.00 P. M.—Is in stuporous condition, completely unconscious, pulse very feeble.

℞ strychnine, sulphate gr. $\frac{1}{30}$ hypo.

Temperature, 103.8°; pulse, 128; respiration, 38.

Died at 8.15 P. M. December 2d, 1896.

EXAMINATION OF URINE.

(Drawn by catheter just before death).

Amount in 24 hours,	Not stated.
Color,	Light straw, clear.
Odor,	Peculiar aromatic, sweetish odor.
Reaction,	Strongly acid.
Specific gravity,	1.024.
Urea,	2 grs. per oz.
Albumen, heat test,	Present.
cold nitric acid test,	Large trace.
Sugar: Fehlings's test,	Very active reaction.
Fermentation test,	3.752 per cent.
Sediment,	Granular casts quite numerous, a few epithelial casts; non-characteristic epithelial cells; bacteria.

The autopsy was performed about three hours after death.

AUTOPSY.

External Examination.—The body is that of an unusually large man. The head is large and oval, the face flat, and the eyebrows are prominent, thick and overhanging. The eyelids are heavy and the lashes long. The nose is short, thick and flat and the end has a globular appearance. The nostrils are large and the alæ nasi are thick and heavy. The lips are thick and heavy and the mucous membrane is markedly everted. The tongue is large, very broad, flat, and thick. The malar bones are large and prominent.

The ears are large, well formed, but project from the head in a striking manner.

The neck is short and thick. The neck muscles are large and well formed.

The shoulders are broad, square, symmetrical, and muscular.

The thorax is symmetrical, well formed, and its muscular development is excellent.

The arms and forearms are well shaped, but the muscular development is somewhat below that of the trunk, and the muscles are rather soft and flabby.

The wrist joints are enlarged and very prominent. This enlargement seems to be entirely bony, and to be one of the distal extremities of the radius and ulna, rather than of the carpal bones.

The hands are short, thick, flat and broad. The muscles are not well formed and the palms are soft and flabby. The thumbs are abducted to nearly a right angle to the median line, and are short, thick, and have a peculiar square distal phalanx. The nails are broad and flat, not thickened or creased. The ends are curved downward. The other digits of both hands show similar characteristics, the distal phalanx in each instance having a peculiar bulbous appearance.

The abdomen, which is symmetrical in form, is distended and tympanitic. The musculature is good.

The pelvis and thighs are large and well formed; the muscles of the thighs are, however, somewhat flabby. The knee joints are proportionally very large and prominent. The patellæ are enlarged and projecting.

The legs are fairly well formed, but the muscles are soft and flabby. The distal extremities of both tibia and fibula are manifestly enlarged, the enlargement being bony in nature.

The feet are heavy and thick, soft, not muscular. The toes are inverted and the heels are drawn up. The plantar surfaces are soft, though bunions are present at the usual points of pressure. The great toe is deflected outward from the median line of the foot. The toes are short, the bases thick, and the distal phalanges have an appearance similar to that of the finger ends. The nails here, as there, are broad and flat, not thickened.

The following measurements were taken:

HEAD.

Occipito-frontal circumference	23½ in.
Fronto-mental	27 in.
Occipito-mental	28½ in.
Across base of nose	1¾ in.
Across alæ nasi	2 in.
Circumference of neck at level of cricoid cartilage	17 in.

Upper Extremities.

	Right	*Left.*
Circumference of elbow joint at level of internal condyle	11 in.	11 in.
Circumference of wrist joint at level of styloid process	7¼ in.	7½ in.
Circumference of metacarpus	10½ in.	10½ in.
" base of thumb	3¾ in.	3⅛ in.
" last phalanx of thumb	3⅝ in.	3¼ in.
" base of first digit	4 in.	3¼ in.
" base of third digit	3 in.	3 in.
" base of last digit	2¾ in.	2¾ in.

Length of Digits.

Thumb	3 in.	3 in.
Forefinger	3 in.	4 in.
Ring finger	4¼ in.	4¼ in.
Little finger	3½ in.	3½ in.

Lower Extremities.

	Right.	*Left.*
Circumference of thigh at groin	22 in.	20½ in.
" of knee joint, over centre of platella	15½ in.	16 in.
Circumference of calf	14 in.	14½ in.
" of ankle at level of internal malleolus	10⅞ in.	10¼ in.
Across dorsum of foot at level of internal cuneiform bone	5 in.	5 in.
Circumference of base of great toe	4¼ in.	4¼ in.

The skin is soft and white, and has a peculiar œdematous appearance over the face. A large amount of fine, crisp, dark hair is distributed over the anterior aspect of the thorax and abdomen, down the back, and over the flexor surfaces of the extremities. The hair on the head, over the pubes, and in the axillæ, is thick, fine, and jet black in color.

At the anterior fold of the right axilla, at about the level of the nipple, is a suppurating nodule of about the size of a pea. It is not indurated, and a lesion very similar in character, is found on the abdomen, in the median line, about two inches below the umbilicus.

The penis is small and the foreskin is long, but it can

be drawn back, exposing the glans, on the surface of which, just below the meatus, is found a circular depressed scar about 0.6 centimetre in diameter. The testicles are firm and of about the usual size.

Rigor mortis is just beginning to be apparent.

Section. The muscles are deeply colored. The blood is fluid. The amount of panniculus adiposus is small.

There are a few old, stringy adhesions over the base of the lung in the left pleural cavity. The pericardium is apparently normal.

Heart.—Weight, fifteen ounces. The cavities are contracted. The amount of pericardial fat is small. The muscle is firm, solid and of good color. A small amount of ante-mortem clot is found in the upper portion of the right ventricle.

Lungs.—The bronchi are deeply congested. The lungs show œdema, with congestion. The peribronchial nodes are somewhat enlarged and are deeply pigmented.

Stomach.—The stomach is greatly dilated and is distended by a large amount of partly digested food, the greater part of which is found to be poorly masticated cabbage leaves. The mucosa seems to be in a fairly normal condition.

Intestine.—There is great gaseous distention of the entire intestine. The capillaries of the peritoneum are injected, and there is a small amount of fibrinous exudate on the surface of the peritoneum. A sac of non-purulent, serous exudate is found encysted about the curve of the sigmoid flexure. General peritoneal adhesions of recent origin are present, most intimate about the caput coli, which is bound down in the right iliac fossa. The appendix, which is about six inches long, is closely adherent to the posterior surface of the cæcum, and is surrounded by much inflammatory tissue. It is not perforated, but is the seat of an active inflammatory process, and contains a considerable amount of fæcal matter. The entire intestine, down to the sigmoid flexure, is completely filled with a soft grayish fæcal mass, containing bubbles of gas. The intestinal mucosa is apparently normal.

Liver.—Weight, eight pounds, five ounces. The liver is enlarged. The capsule is smooth and is not thickened. The tissue is firm but granular. It is a light grayish-brown in color. The lobules are well marked. The perivascular connective tissue is apparently not increased in amount.

Spleen.—Weight thirteen ounces. The spleen is enlarged; it is bound by recent adhesions to the cardiac end of the stomach. The capsule is considerably thickened, and is covered by small fibrinous masses. It is flabby in consistence and chocolate in color.

Pancreas.—The pancreas is large, firm and of a normal pink color.

Adrenals.—The adrenal bodies are large and well formed; they show no apparent lesion.

Kidneys.—United weight, one pound eight ounces. Both kidneys are greatly enlarged. The capsules are thickened and slightly adherent. They are dark pink in color. The cortex is thin. The markings are distinct and regular. The tissue is very granular and friable. The bases of the pyramids are deeply congested. The vessels are distended. Both pelves are dilated with urine.

Ureters.—The ureters are large but apparently normal.

Bladder.—The urinary bladder is large. It contains a small amount of clear urine. The wall is thin, and it has evidently been greatly distended.

Head.—There is a scar on the scalp, of about the size of a silver half-dollar. It is located five centimetres to the right of the median line and on a line drawn perpendicularly between the two mastoid processes. The bones of the calvarium are greatly thickened. The amout of cancellous tissue is proportionally small. The skullcap is symmetrical and well arched.

Meninges.—The dura is not thickened or adherent. The vessels of the membranes are congested, the congestion being most marked over the frontal lobes. There is a moderate amount of submeningeal œdema. The pia is slightly adherent, especially over the frontal lobes.

Brain.—The brain is large and symmetrical. The

convolutions are well marked and the sulci are deep. The brain tissue is firm and solid. The vessels are considerably congested throughout the entire brain. The ventricles contain the usual amount of normal fluid. No lesion is evident in either cerebrum, cerebellum, bulb, or along the floor of the ventricles.

Pituitary Body.—Crowning up from the pituitary fossa and inclining toward the left, is found an ovoid red mass, measuring 1.5 centimetre, from before backward, and 0.7 centimetre, from above downward. It is attached below, apparently, to the pituitary body. The mass is of a soft, jelly-like consistence, and is quite vascular. It is found to press directly on the left optic tract, just posterior to the chiasm. The tumor is attached by a stalk to the hypophysis, which is enlarged to about five times its usual volume. The pituitary fossa is greatly enlarged, and the bones making up its wall are abnormally thin. No adhesions exist between the pituitary body or tumor and the surrounding tissues.

Thyroid Gland.—The thyroid gland is symmetrically enlarged. It is dark-red in color, firm in consistence, and contains a few cysts filled with a gelatinous material.

Thymus.—The thymus gland is found to persist. It is symmetrical in form. Each lobe measures, from above downward, about six centimetres, 2.5 centimetres in breadth and about 1.7 centimetres thick at its largest portion. The tissue is firm. The color is a light pink.

Sympathetic Ganglion.—The ganglia of the sympathetic system are large and distinct.

As the viscera were removed from the body, bits of each were selected for microscopic examination. These tissues were placed in the ice box for the remainder of the night (five hours) after which they were placed in various hardening fluids; each tissue being preserved by at least two different methods. The majority of the tissues were hardened in five per cent formalin,—Müller's fluid and Lang's solution. After the tissues had become sufficiently fixed they were embedded and cut. Both collodion and paraffine sections were made of the more important tissues,

but the larger part of the work was done on paraffine sections, varying from one and one-half to six μ in thickness. Various staining methods were used as indicated by the fixative and by the special tissue,—hæmatoxylin and eosin and Van Gieson's hæmatoxylin and picro-acid-fuchsin were used as routine stains.

MICROSCOPIC EXAMINATION.

Voluntary Muscle (*Biceps and Quadriceps Extensor*).—The size of the muscle fibres varies considerably. Cross striation is very distinct and regular. The nuclei of the muscle cells are greatly increased in number; they are found arranged beneath the sarcolemma, mostly in groups of three to five. The nuclei are irregular in shape and frequently show karyokinetic figures. The endomysium and perimysium are increased in their amount.

Bones.—Examination of sections of the hypertrophied bones, shows a simple increase of the normal bony constituents. The cancellous tissue is relatively in less amount than is usually the case.

Heart-Muscle (*Wall of Left Ventricle*).—The muscle cells are narrow, apparently atrophied. The striation is distinct. Some of the muscle cells show small areas of light staining material at either pole of the nucleus and in these areas a deposit of fine brown pigment is frequently seen. No change is apparent in the cell nuclei. The interstitial connective tissue is considerably increased in amount. Its cell nuclei are numerous and they stain deeply with hæmatoxylin. In places, fine brown pigment granules are found scattered throughout the connective tissue. The nuclei of the perivascular connective-tissue cells are evidently in a state of active division. The arteries and capillaries are dilated, and the smaller arteries show endarteritis of a marked degree.

Lungs.—The connective tissue beneath the pleura is greatly thickened. The air sacs of the lung are mostly distended and in places they have ruptured one into the other, in such areas considerable atrophy of the alveolar

walls has taken place. Many alveoli contain plugs, made up of red and white blood cells, held in a mesh of fibrin; these plugs have, for the most part, separated from the walls of the alveoli. The leucocytes, found in these clots, are charged with coarse, brown pigment granules. A similar pigment is found scattered diffusely throughout the entire section. The vessels of the bronchi are injected and the connective tissue surrounding the bronchi is increased in amount. The blood vessels are distended and congested with blood. The lymphatics and lymph-nodes contain large amounts of a coarse, dark pigment (anthracosis).

Liver.—The outlines of the liver cells are irregular. They are considerably atrophied. The cells are filled with coarse highly refractive granules and contain many large oil sacs; in some places these oil sacs are so large that the entire cell is taken up by two or three oil globules to the exclusion of the nucleus. By far the larger number of the cells contain an extensive deposit of a fine brown pigment. Some of these pigment granules give a reaction for iron, with the potassium ferro-cyanide-hydrochloric acid test, while others of the granules do not respond but stain a faint green with methylene blue. This pigmentation is most extensive about the intralobular veins. The nuclei of the cells are, for the most part, in apparently normal condition, but in some of the more extensively diseased cells, they refuse to take the nuclear stains, and are, in places, completely disintegrated. The cells about the intralobular veins show the most extensive disease. The bile capillaries appear to be very large, perhaps due in part to the atrophy of the liver cells. The blood vessels are distended and congested, some of the larger ones show an increase in the subendothelial layer of connective tissue. The perivascular connective tissue is increased in amount and it is in a state of active proliferation. The bile ducts of the interlobular spaces are apparently increased in number.

Spleen.—The interstitial connective tissue throughout the entire section is increased in amount. The walls of the

blood vessels are thickened, and a few show proliferation of the cells making up the intima. The capillaries are distended with blood and, in places, quite extensive extravasations have taken place. There is a large amount of granular structureless material scattered about between the cells. This substance reacts to acid dyes. There is a granular deposit of a brown pigment scattered throughout the entire section, and most of the splenic cells contain considerable masses of this pigment. It is also found scattered throughout the fibrous reticulum of the organ and even in the walls of the blood vessels.

The size of the pigment granules varies from a fine dust, to masses one-fourth the size of the nucleus of a splenocyte. When acted upon by potassium ferrocyanide and dilute hydrochloric acid, some of those granules become an intense blue, but the majority fail to react and retain their original brown color.

Pancreas.—There is a great increase in the amount of interstitial tissue. In some places the alveoli are almost completely obliterated by growth of this tissue about them; in other areas, where the alveoli have been even less pressed upon, atrophy of the alveolar cells has taken place. Many cells show parenchymatous degeneration, and these cells do not react to dyes in a normal manner.

Adrenal Bodies.—No changes from the normal are evident.

Kidneys.—The interstitial connective tissue is universally greatly increased in amount. Many nuclei of the connective-tissue cells show karyokinetic figures. The capsules of Bowman are all more or less thickened, so much so that in places the Malpighian bodies are marked by whorls of connective tissue only. The perivascular connective tissue shows great hypertrophy. The walls of the smaller arteries are much thickened. The vessels are dilated and are filled with blood cells, this is especially true of the capillaries of certain Malpighian tufts where the distension is very great. Granules of brown pigment substance are found scattered throughout the connective

tissue wherever found, in the capsule of the kidney itself, about the vessels and even in their walls. The size of the pigment granules varies, from a fine dust-like deposit, to masses of considerable size. The cells of the convoluted tubules are irregular in contour; many are partly broken down. They are filled with large granular masses of a material, staining a faint pink, with eosin, and the lumen of the tubule is often filled by a debris, similar in appearance. The roded striation of the cells has almost entirely disappeared and the outer one-third of the cell is occupied by a zone of faintly staining material and by a band of fine, brown pigment, extending up nearly as far as the cell-nucleus, and sharply differentiated from the inner two-thirds of the cell, which contains the granular material mentioned above and also occasionally, oil sacs of considerable size. The nuclei of these cells are distinct and regular; they respond well to nuclear dyes. The cells of the loop of Henle show the same granular degeneration as those of the convoluted tubules, but here the pigment is diffusely scattered throughout the entire cell protoplasm. The cells of the collecting tubules are regular in contour and normal in their staining reactions. Large masses of the pigment substance are sometimes seen in their protoplasm, where, in most instances, it is arranged in crescentic masses at the poles of the nucleus. The large bodies of pigment substance found here are in marked contrast to the dust-like deposit seen in the cells of the convoluted tubules. When treated with potassium ferrocyanide and dilute hydrochloric acid, a portion of the pigment gives a reaction for iron, but for the most part it remains unchanged.

Testis.—No pathological changes are evident in sections of this gland. Some of the tubules show the various stages of spermato-genesis in a beautiful manner. Cross-sections of the vas deferens show it to contain numerous well formed spermatozoa.

Mesenteric Lymph Node.—The connective tissue stroma of the gland is apparently increased in amount. The walls of the blood vessels which are included in the sec-

tions are thickened, and the vessels are congested. The gland is deeply pigmented. The pigment granules are scattered throughout the stroma of the gland, and are also found in considerable quantity in the lymph cells themselves.

Arteries.—Sections of the right carotid artery and other of the larger vascular trunks show occasional areas of thickening of the subendothelial connective tissue layer. The walls of the arteries show almost universally a thickening of both tunica media and adventitia, fibrous in character.

Semilunar Ganglia.—Sections stained with the Nissl methylene blue, and by the eosin-Nissl-method show degenerative changes, of various degrees, in many of the ganglion cells. Some cells stain in a perfectly normal manner, while in others the plaques are stained irregularly and in still others, not at all. Many of the ganglion cells contain pigment of a dark brown color; part of these pigment granules take on a greenish tinge, after staining with methylene blue. Fine granules of the pigment are found scattered everywhere throughout the sections of these ganglia.

Peripheral Nerves.—Sections of various peripheral nerves, stained with hæmatoxylin and eosin and by Weigert's method, show no apparent changes from the normal.

Brain, Medulla and Cord.—The cerebrum, cerebellum, pons, medulla and the upper cervical segments of the cord were hardened in Müller's fluid. Sections were cut from nearly every portion of each, and were stained with carmine and by the Weigert method. Unfortunately this fixative would not admit of the use of the Nissl stain. The only changes found were those of the vascular system, where the vessels were seen, universally, to have thickened walls and to be greatly congested.

Left Optic Nerve.—In sections hardened in Müller's fluid and stained by Weigert's method, most of the fibres react to the stain in a normal manner, but occasional strands are found, in which degenerative changes are

evident, in so far as we may rely on the methods used to determine them. The arteria centralis retinæ and its branches are distended and filled with blood cells.

Retina.—Sections hardened in Lang's solution were stained with Nissl's methylene blue to bring out the structure of the ganglion cells. The large multipolar ganglion cells took the stain in a very beautiful manner. The plaques are regular in arrangement and normal in their staining reactions. The nuclei of these cells are, however, somewhat swollen and a little less clear than should be. The subepithelial and stellate ganglion cells stain, for the most part, in a perfectly normal manner but occasionally one is found in which the plaques have taken the stain poorly. The nerve fibre layer, so far as can be determined by the method used, (Müller's fluid hardening and Weigert's stain) shows no degenerated fibres.

Thyroid Gland.—The structure differs in no respect from that found in the perfectly normal gland.

Thymus Gland.—The structure is apparently normal. Hassall's corpuscles are numerous. The lymph adenoid elements are regularly arranged and stain normally. The connective tissue stroma is quite small in amount but appears, in places, to be recently formed. The blood vessels and lymphatic channels are very numerous. There is no fatty infiltration nor any other evidence of degeneration. The gland has the appearance of being in a state of activity. Both connective tissue and lymph adenoid cells show occasional karyokinetic figures.

Pituitary Body.—The enlargement of the pituitary body is found to be of the anterior glandular lobe only. The posterior lobe is apparently normal both in size and in structure. The tissue of the hypertrophied anterior lobe does not invade that of the posterior. The structure of the greatly enlarged prehypophysis differs, in general, but very little from that of the normal. It is surrounded by a thin capsule of fibrous connective tissue and beneath this the cells are arranged, for the greater part, in columns separated by longitudinal strands of connective tissue, gradually proceeding toward the centre; these columns of

cells assume an alveolar arrangement and the connective tissue stroma becomes less apparent. The gland-like arrangement of the cells is, perhaps, somewhat less distinct than in the normal, but it is, nevertheless, perfectly apparent. Alveoli, containing colloid material, are found in small number. They are located in the zone bordering between the anterior and posterior lobes. The colloid, contained in these areas, stains blue with hæmatoxylin and brownish yellow with Van Gieson's stain. The tissue is rather more highly cellular, than is the case in sections of the normal prehypophysis and, in certain areas, they are very closely grouped together.

The cells which make up the aceni, are, as in the normal hypophysis, of two distinct varieties; the one large, usually oval in shape and with very granular protoplasm, which responds to eosin; the indigo, in Merkel's stain, and to picric acid in the ordinary picro-carmine stain. The other variety is more columnar in form, as a rule, smaller, and the protoplasm is but slightly granular. These cells respond in a less characteristic manner to stains, usually giving a bluish tinge with hæmatoxylin and eosin, and a faint carmine color both with Merkel's stain and picro-carmine. The last mentioned, or the chief cells, make up the walls of the alveoli for the greater part; each alveolus, however, usually contains from one to three cells of the chromophilic type. But in these areas where the cells are found most closely grouped together the chief cells are in by far the greater number. Isolated aceni, made up entirely of chromophilic cells, are also found diffusely scattered about among the alveoli of chief cells, throughout every section. Cells of both varieties containing distinct karyokinetic figures, are frequently found and evidently both kinds are actively proliferating.

Areas of granular débris are found scattered throughout the sections. The protoplasm of the cells bordering on these areas, often shows evidences of breaking down, and the débris itself responds, as a rule, to those stains which are taken up by the protoplasm of the chromophilic cells. A few granules, of a fine brown pigment substance,

are found scattered about in the sections. The blood vessels are rather less prominent in these sections than in those of normal hypophyses, but they are still very numerous. Connective tissue stroma is also in less quantity than in normal sections.

The tumor is found to be attached to the prehypophysis by a short stalk of tissue which has a structure similar to that of the anterior lobe. The tumor mass is surrounded by a thin, fibrous tissue capsule and its structure varies, in no respect, from that of the hypertrophied prehypophysis.

In the study of the enlarged pituitary body and of the tumor attached to it, constant comparison was made with sections of normal hypoyhyses, which had been prepared in the same manner as those of the case under study.

SUMMARY.

A brief statement of the more important lesions found in the case, is as follows:

General enlargement of the body, more or less symmetrical; in short, gigantism.

Enlargement of the bones of the face, of the terminal phalanges, and of the epyphisial extremities of the long bones.

General connective tissue hyperplasia.

Hypertrophy of the thyroid gland.

Persistence and hypertrophy of the thymus gland.

Hypertrophy of the anterior lobe of the pituitary body and a hyperplastic tumor attached to the prehypophysis.

Degenerative changes in the liver and kidneys.

Atrophy of the pancreas.

A deposit of pigment substance everywhere, throughout the entire body.

Congestion of the blood vessels and thickening of their walls.

Degeneration of the ganglion cells of the solar plexus.

The case seems to be typical of acromegalia, in every respect, possessing, as it does, nearly every symptom,

physical sign and anatomical finding, which has been described as characteristic of this disease. One exception should be mentioned, kyphosis, or some other like deformity of the spinal column, has been found in most of the cases reported; such deformity was entirely absent in this case.

The manner of death, looked at from the point of symptomatology only, seems to be that usually present in acromegalia, but, from the anatomical findings, we must conclude that the probable cause of death was a low form of peritonitis acting on an organism whose vitality had been greatly depressed by the long-standing general disease.

Glycosuria has often been reported in acromegalia, but, in this case, it appears to be associated with certain anatomical findings which have not before been reported in acromegalia, at least to the knowledge of the writer, and which incline one to the opinion that this case is complicated with another and very characteristic condition. The marked pigmentation of all the tissues, especially of the liver, kidney, spleen and lymphatic glands; the hypertrophic cirrhosis of the liver and spleen; the atrophied cells and interstitial tissue hypertrophy of the pancreas; together with the presence of a low form of peritonitis and the glycosuria present a picture quite typical of "Diabète Bronze," described by Marie. A closer study of the pathological findings will, the writer believes, thoroughly establish the co-existence of this malady, together with the acromegalia in this case. It is, however, foreign to the object of this paper to discuss this condition, and, in the consideration of the case, these features will be disregarded.

The marked congestion of the blood vessels, throughout the entire body, and the degeneration of the ganglion cells of the semilunar ganglia are, perhaps, due to the terminal infection which appears to have been the direct cause of death.

Chapter II.

CASE II.

The patient, a female, entered the Montefiore Home on October 16th, 1896. She remained here up to the time of her death and was constantly under the observation of Dr. Joseph Fraenkel and his assistants to whom I am indebted for the following history of the case:

Name, M. S——. Admitted October 16th, 1896. Age 37. Nativity, Germany. Married. Time in U. S., fourteen years. Has lived in New York fourteen years. Clinical diagnosis on admission, diabetis mellitus.

The patient was born in southern Germany, of Jewish parents. Father, who was thought to be consumptive, died of pneumonia; mother of heart failure; four brothers and sisters living; four dead. Had three children, all of whom died in very early youth. None reached the age of one year. No miscarriages. Thinks husband is dead; has not seen him for two years. She does not recollect any disease of childhood; first menstruation at eighteen; was regular up to last February, when menstruation ceased. Claims to have been well, up to her first childbed, about eight years ago. Then had a difficult labor and was torn during delivery. General symptoms followed for six years. She went to doctors, but got no relief. Was operated upon by Dr. Munde three years ago in Mt. Sinai's Hospital. Afterwards, she suffered from general malaise and she thinks that she had malarial fever. She went to the Gouverneur Hospital in April, 1896, and was operated upon again. She was then told that she had diabetes.

PRESENT HISTORY.

The patient now complains of general weakness in the limbs, pain in the back, increased appetite, polydipsia, dryness of the throat, with an occasional cough, frequent micturition, especially at night; pruritus and "hot flesh."

Examination.—Pulse, 96, somewhat hard. Temperature, 98°. Respiration, 18. Weight, 134 lbs. The patient

is short, darkly pigmented and prematurely gray. The abdomen is large. She says this has been present since she began to drink so very much. On percussion left anterior, slight dullness is found in the supraclavicular space; dullness extends to external axillary, and dullness is also present at base, posteriorly. Percussion boardy, on the right side. Heart normal. Liver slightly enlarged, hard, left lobe feels irregular. Abdomen, distended; it measures 85 c.m. at the level of the umbilicus. Tympanitic percussion on sides, no fluctuation. On auscultation some spots of diminished breathing. Over the arteries a muffled sound with a faint murmur is heard.

Bedside Notes.

November 16, 1896.—Complains about polyphagia; frequent urination and polydipsia; night sweats; dryness in throat; severe pruritis.

June 20, 1897.—Urine of peculiar smell, yellow, slight greenish tint; acid, spec. gr., 1046; no albumen; sugar present.

June 23, 1897.—Urine of the same peculiar smell; sticky; sp. gr., 1040; acid; considerable amount of sugar.

Some pain and heaviness in left lower extremity; at present has severe pain in right hypochondrium; pruritis; excessive sweating at night. Only occasional headaches, but when present very severe. Polydipsia; polyuria; increased appetite. Hyperæsthesia of extremities to touch; pain in back. She thinks that the fingers have been getting broader during the past year.

Physical Examination.

June 23, 1897.—The patient is short of stature; good muscular development, but rather poorly nourished. The hands and feet are short. The nose and chin reminds one slightly of acromegalic features. The skin is slightly yellow in color; it is moist. The mammæ are atrophic. Over the back, effects of scratching are seen but there are no scars noticeable. Abdomen is bulging. The head is well shaped and, except for the above mentioned features present in the face, nothing especially noteworthy is seen. The skin of the face is moist and glossy. The ears are well formed. The palate is asymmetrical. Skull not tender to percussion. There is no apparent diminution of the visual fields. Hearing normal. Smell and taste unimpaired.

The pupils are well shaped and of equal size. Light and concensual reactions present; accommodation perverted; convergence,

(insufficient); ocular excursions good. Pulse, 100, rather small volume; respiration, 20: respiratory excursions on both sides equal; temperature, 98.5°.

Both facial nerves normal. No chin jerk. Sensibility of face intact. The tongue is somewhat enlarged, but not very much. It is heavily coated and somewhat tremulous. The pharyngeal reflex is lively. In pharynx, collections of pus are present. The teeth are bad, especially those of the upper jaw. The neck is short, but well built. The thyroid cannot be palpated. The chest is well built, slight depressions above and below clavicles noticeable. Apex beat, fairly palpable. The vertebral column is of normal configuration and not tender to pressure.

Percussion—Left Anterior.—The note is higher pitched and there is movable dullness at the upper border of the fourth rib. *Axillary.* There is an immovable dullness at the seventh rib. *Posterior*—Movable dullness at the level of the tenth, and the note here is higher pitched. *Right Anterior.* The note is higher pitched, and there is movable dullness at the upper eighth; *posteriorly* there is movable dullness at the level of tenth. There is dullness in middle portions of the sternum. Heart dullness is increased, it seems, to the left, but it is rather difficult to make it out exactly.

Auscultation.—The respiratory murmurs are rather diminished and indefinite, especially so over the left lung. The heart sounds are muffled and this muffling amounts to a blowing murmur at the third intercostal space, left side. Epigastric reflex present on left, absent on right. Abdominal reflex present on right, absent on left.

Upper Extremities.—No marked abnormality in aspect; no tenderness to pressure; no sensory disturbances; reflexes of moderate force, elicitable.

Spleen.—Not enlarged to percussion or to palpation.

Liver.—Seems considerably enlarged to percussion, especially the right lobe. Palpation of liver is painful, but nothing further can be made out by palpation.

Abdomen.—Lateral parts of abdomen give dull percussion note, which is not dependent on position. No evidences of ascites.

Lower Extremities.—Present little abnormality of aspect. Not tender to pressure. No paralysis. No sensory disturbances. Plantar reflexes absent. Patellar reflexes lively, more so on the left than on the right; Achilles jerks present.

October 6, 1897.—Died in coma.

From the time of this last examination, up to the time of death, October 6th, 1897, both Dr. Fraenkel and the assistant physicians at the Montefiore Home were able to note marked progressive enlargement of the hands and

feet, and the digits began to take on, to a certain degree, the characteristic "sausage shape," while the facial peculiarities, already noted, became exaggerated so that the diagnosis of acromegalia was definitely determined upon.

The accompanying photograph of the patient, (Plate I, Fig. 2) which was taken some three years before death, shows a coarseness of feature, of a type merging on the acromegalic. Unfortunately, as death occurred somewhat unexpectedly, Dr. Fraenkel was unable to obtain photographs during the later stages, when the facial characteristics became much more marked.

Death took place apparently in diabetic coma.

The body was immediately removed to the hospital morgue, where it was kept surrounded by ice until the time of the autopsy, which was performed about eight hours after death, by Dr. Henderson B. Deady, of the Pathological Institute, and the author.

The anthropological measurements were taken at the time of autopsy by Dr. Hrdlicka, Associate in Anthropology of the Institute.

AUTOPSY.

Montefiore Home. Case No. 772. 10.00 P. M., October 6th, 1897.

External Examination.—The body gives one the impression of being short and stocky. The abdomen is pendulous. The shoulders are thrown forward. The neck is short, thick and heavy. The breasts are flabby and pendant; their areolæ are large and but slightly pigmented. The feet are short and full and the toes have a peculiar square-like terminal phalanx. They do not appear out of proportion to the shafts of the legs, which are well formed. The arms are well formed. The hands are large, but not markedly so. The thumbs are somewhat deflected outward and they have squared distal phlanges.

The face is striking in its general impression. The forehead is prominent and the frontal eminences are pronounced. The eyebrows are heavy. The malar bones

are large and prominent. The nose is heavy. The alæ nasi are thick. The end of the nose is broad and flat and has a crease extending down over its centre. The lips are thick and everted. The corners of the mouth droop. The mucous-membranes are anæmic. The tongue is broad and flat, though thin. The alveolar arches show many missing teeth. The teeth of the lower jaw project but slightly beyond those of the upper. The symphysis of the inferior maxilla, however, shows marked prognathism. The ears are large, but well formed.

The labia majora and the nymphæ are large and deeply pigmented. The clitoris is larger than usual; its glans is well exposed.

The skin of the face is of a peculiar greenish cast and reminds one of that of a mulatto. Over the face and upper thoracic region, the skin is rough, while over the other parts of the body it shows no marked peculiarity. The nails of both toes and fingers are curved, thin and well formed.

The hair of the head is abundant and fairly long; it is thrown into wavy curls and, while black, is tinged with gray. It is similar in appearance to the hair of a mulatto. The eyebrows and lashes are heavy, but not markedly so. The hair found in the other usual places of distribution, is fine, slightly curly and black in color. No abnormal distribution.

The face and hands are of the acromegalic type and the general appearance of the body inclines one to this diagnosis, but, unless the peculiarities are known to have been progressing, we must look on such a diagnosis with question.

MEASUREMENTS.

Height	1.53	metre.
Width of the shoulders	36.7	cm.
Width of thorax opposite the 3d articulation	24.7	cm.
Diam. bitrochanteric (touching lightly the skin)	34.1	cm.
Distances: Vertex to sternal notch	29.3	cm.
" xiphoid	48.7	cm.
" umbilicus	64.8	cm.
" pubis	79.0	cm.

Centre of the sole to the fibular articulation, on left	30.9	cm.
Centre of the sole to the great trochanter	77.8	cm.
Head: Circumference max.	57.2	cm.
(Hair not very profuse).		
Arc: Root of the nose to the ext. occ. protub.	35.2	cm.
Diam. frontal minim	10.8	cm.
" bizygomatic max.	14.0	cm.
" bigonial (of the lower jaw)	10.6	cm.
Height of the face: Chin to the hair line	19.4	cm.
Chin to the root of the nose	13.2	cm.
Nose: Height	4.9	cm.
Width	4.0	cm.
Index	81.6	cm.
Thickness of lips	1.9	cm.
Length of lips	5.0	cm.
Height of left ear	5.5	cm.
Breadth of left ear	3.8	cm.
Hands and feet:		
End of radius to end of medius, left hand,	15.8	cm.
Diam. transv. of the hand at the phalangeal articulation	7.5	cm.
Thickness of palm above the knuckles, compass firmly applied	2.5	cm.
Length of medius, intern. surf. from the line at its root to its tip	6.8	cm.
Its circumference over the first phalanx	6.9	cm.
Diam. later. at 2d phalanx middle, touching skin slightly	2.1	cm.
Diam. ant. post. at same place	1.7	cm.
Total length of foot	22.3	cm.
Width at phlang. metatarsal art.	8.9	cm.
Thickness at same, instrument firmly applied	2.6	cm.
Circumference of the foot at the instep	24.0	cm.
Circumf. of leg, min.	21.0	cm.
Circumf. of wrist	16.0	cm.
Thickness of the skull-cap over the frontal eminences	1	cm.
Mean thickness over the parietals	6	cm.
Mean thickness over the occipital, above	1	cm.

Section.—The skin is apparently normal in thickness. There is a small amount of sallow colored panniculus adiposus. The muscles of the thorax and abdomen are of fairly good volume, but are somewhat soft. They are of a pale brown color.

The pleural cavities are free.

The pericardium is negative.

Heart.—The heart is large. The epicardium is thickened and opalescent in areas, its capillaries are congested and, along the course of the larger vessels, notably of the descending trunks of the coronaries, are numerous punctate hemorrhages which apparently represent small emboli. The aortic and mitral segments are thickened and are covered with small diffuse areas of calcareous deposit. The walls of the coronary arteries are greatly thickened. They show a moderate amount of arteriosclerosis. The heart walls are thin, the cavities are dilated. The muscle is soft and light brown in color. The left ventricle contains a small amount of post-mortem clot. Circumference of aortic ring at the base of valve flaps, 7 cm. Arch of aorta 3 cm. above valves 6.5 cm. in circumference. The aorta shows greatly thickened walls, with considerable areas of endarteritis. Weight of heart, 330 gm.

Respiratory Tract.—The trachea and bronchi are of small calibre. Their mucous membrane is congested and it is covered with slimy mucus. The large bronchi show, in places, a considerable increase in the amount of connective tissue surrounding them. The peribronchial lymph nodes are slightly enlarged. The lung tissue shows, in general, extreme congestion. The pharynx is deep and capacious. Both tonsils are prominent.

Tongue.—The tongue is broad, proportionately short and thin. Its superior surface is rough. Teeth marks are not present. Measurements, from base of epiglottis to tip of tongue, 10.2 cm. Maximum breadth of tongue, 7.6 cm.

Epiglottis.—The epiglottis is short, blunt and broad. Length 1 cm. Max. breadth 2 cm. The thyroid cartilage is small. It is symmetrical in shape.

Thyroid.—The thyroid gland is enlarged, the right lobe considerably more so than the left. The isthmus is small. Weight of gland 35.5 gm.

Aortic Arch.—The arch of the aorta shows considerable thickening of the walls of that vessel. The intima shows quite extensive diffuse endarteritis. Circumference of arch at centre 6.5 cm.

Thymus.—There are a few nodular masses of tissue found over the arch of the aorta, in the usual location of the thymus gland, which are thought to be persistent portions of that body. These masses contain too much fat and connective tissue to render weighing of value.

Peritoneal Cavity.—The intestinal coils are distended with gas. The caput coli is free, but the appendix is long and passes through its own, then perforates the mesentery of the cæcum, so that its tip finally rests on the posterior surface of the caput coli.

Both large and small intestine appear to be in a natural condition.

The mesenteric lymph nodes are not enlarged.

The stomach is small, no lesion is evident.

Liver.—The liver is greatly enlarged. It is symmetrical in shape. The capsule is smooth but is generally thickened. The tissue is very firm in consistence. The cut surface is granular. The color is light brown. The lobules are very plainly marked out and the interstitial tissue is increased, but apparently contraction has not yet taken place. Weight of liver 3,000 gm.

The gall bladder is distended with dark fluid bile. Its duct is patent.

Spleen.—The spleen is enlarged. The anterior border is deeply cleft. The capsule is thickened and is covered by minute granulations. The tissue is of a dark chocolate color. The Malpighian bodies are prominent and the interstitial tissue is apparently considerably increased. Weight 260 gm.

Pancreas.—Large. The tissue is very firm. It is light pink in color. Apparently the interstitial stroma is increased and the islands of the gland tissue are quite widely separated by bands of connective tissue. Weight of pancreas 140 gm.

Adrenals.—Both are large and symmetrical in shape. No lesions are evident. Weight 7.5 gm.

Kidneys.—The kidneys are surrounded by a moderate amount of perinephritic fat and connective tissue. The kidneys are enormously and symmetrically enlarged.

The capsule is smooth, but thick and densely adherent. The cortex is thin and regular; the markings are distinct. The cut surface is very granular. The capillaries are congested. The color is a yellowish pink and the consistence is very firm. The perivascular connective tissue is increased in amount, indeed the whole kidney substance seems much hypertrophied. Weight of each 320 gm.

Ureters.—The ureters show no lesion.

Bladder.—The bladder is capacious; it contains about 200 cc. of clear, light colored urine. The mucous membrane is apparently normal.

Internal Genitals.—The uterus and its appendages are free. The ovaries are large, but their tissue shows general atrophy. The tubes are in a natural condition. The uterus is slightly enlarged. The cervix shows a small stellate tear. The uterine cavity is large. The mucous membrane is atrophic. The muscle is soft and of a light yellow color. Measurements: Fundus to cervix 7.2 cm.; maximum breadth of fundus 5 cm.; maximum thickness of the uterine wall, at the fundus 3 cm.

Head.—The skull-cap shows considerably thickened walls, especially in the frontal and parietal regions (see measurements of) and the amount of cancellous tissue in the bony walls is proportionately increased. The skull-cap is fairly symmetrical and the arching is regular and fairly deep. The depressions for the middle meningeal arteries are deeper than is usually the case. The Pacchionian bodies are not numerous, but they are deeply embedded in the bone.

Membranes.—The dura mater presents no lesion. The capillaries of the pia mater are somewhat injected and the membrane is slightly adherent in places.

Brain.—The brain is large and symmetrically formed. The convolutions are somewhat narrow but are regular. The sulci are deep. The vessels of the base show considerable areas of arterio-sclerosis, and the walls of these vessels are universally thickened. No gross lesions are found in any part of the encephalon.

Base of Skull.—The fossæ of the base are deep, espe-

cially the mid-fossæ and the depressions for the olfactory lobes. The basilar process of the occipital bone is reflected upward, at an unusually acute angle, and the posterior clinoid plate and processes project up prominently. The sella turcica is filled with a firm, solid, bulging mass, which presses on the optic chiasm, as it crosses over its front. The chiasm is greatly flattened, and the optic nerves, as they emerge from the chiasm, are flattened and soft.

The infundibulum projects upward and backward from the centre of the sella turcica. Its stalk is considerably thicker than is usually the case. Diameter of stalk, 3 mm.

Pituitary Gland.—On removing the membranes, the pituitary body is found to occupy the considerably deepened and enlarged sella turcica, causing the bulging, before mentioned. On removal, the pituitary body is found to be enlarged. It is symmetrical in form, firm in consistence, and cherry red in color. The posterior lobe is apparently not enlarged. On cutting into the hypertrophied hypophysis, it is found to be distended by a distinct tumor mass of the same general shape as that of the pituitary body, though somewhat more round in its transverse aspect, and measuring at the centre 15 mm. in diameter. The tumor is yellowish-white in color and is distinctly marked off by the surrounding shell of deep red tissue. The tissue of the tumor is firm and no traces of a central cavity are present. Breadth of pituitary body 27 mm. Greatest diameter at the centre of body 20 mm.; weight 2.154 gm. The walls of the sella turcica, including the posterior clinoid plate, are found to be very thin. The posterior clinoid plate itself is deflected slightly to the left and its processes rise to a level 7 cm. above that of the anterior clinoids. The bone of the plate is perforated by several small vessels, which enter the pituitary fossa in this manner. There is a small bony arch on the posterior surface of the clinoid plate, terminating at a point midway between the posterior processes, in a small tuberosity. Depth from the level of the posterior clinoid processes to the floor of the sella turcica 17 mm. Breadth of floor 18 mm.

MICROSCOPIC EXAMINATION.

Tongue.—(Sections from tip and middle portion).—The epithelium and the papillæ of the dorsum show no changes from the natural, but the subepithelial connective tissue, surrounding the vessels of this region, shows active cell-proliferation. The cells of the connective tissue framework of the body of the tongue, are large and very numerous and the chromatin elements of the cell-nuclei stain with notable distinctness. The fibrillary portions of the stroma are also considerably increased. This connective tissue proliferation is most marked about the blood vessels. The muscle fibres, making up the body of the tongue, vary in breadth from very narrow to broad. Nearly all the fibres show cross striation very distinctly. A coarse longitudinal striation is also present in some fibres (Formalin fixation). Occasional fibres are seen, which show a granular degeneration of the sarcoplasm and, in these, striation is not evident. The nuclei of the muscle-cells are very numerous. They are mostly round, or oval, in shape, and they are found for the greater part, arranged in rows, sometimes of as many as five to seven nuclei, extending in the axis of the fibre. The proliferating nuclei are also found less commonly in groups of three or four. These nuclei show frequent karyokinetic figures. Nearly all the muscle fibres contain a greater or less amount of coarse, granular, brown pigment which is scattered diffusely throughout the fibre, without regularity of arrangement.

Heart.—The heart-muscle cells are small and irregular in shape. Cross striation is well marked, even in those cells which show extensive atrophy. The cell protoplasm is granular and, in places, small vacuoles are found in it. In some of the cells only a small amount of protoplasm remains about the nucleus, and an occasional nucleus is found free in the section, being completely divested of its enveloping cytoplasm. An occasional cell shows a fine, brown pigment-substance gathered about the poles of the nucleus. The nuclei of the cells are very irregular in

shape, some of them exhibiting most fantastic forms. A single cell is occasionally found to contain two, and even more, nuclei. A nuclear membrane is plainly visible in most cases. The structure of the nuclei varies considerably. A good many of them contain nucleoli; in some, the chromatin elements are closely gathered together and deeply stained, showing, in places, typical karyokinetic figures, while in other nuclei, scarcely any structure is to be made out. The interstitial connective tissue of the heart is greatly increased in amount and it is highly cellular. The increase is most noticeable about the blood vessels. The intima of many of the blood vessels, especially of the larger capillaries, shows proliferation of the endothelial cells. Some of these cells are found which show beautifully distinct karyokinetic figures.

Lungs.—A few of the air sacs are found dilated and with thin walls, which have ruptured into adjacent air spaces. An extravasation of blood is present in an occasional alveolus, but the walls of the air sacs are free from any evidences of inflammation, and the blood is evidently accounted for by the general condition of passive congestion. The connective tissue about the vessels is increased in amount, while that about the small bronchi is in usual quantity. There is a small deposit of black pigment in some of the perivascular lymph spaces.

Liver.—The capsule of the liver is thickened and the cells of the connective tissue portions are evidently proliferating. There are a few granules of coarse, brown pigment beneath and in the capsule. The perivascular connective tissue, throughout the section, shows a slight increase. The capillaries are dilated, but contain only an occasional blood cell. The bile ducts show no change. The bile capillaries are widely distended, and some of them contain particles of a green, pigment substance, probably biliary. A few of the cells jutting on such capillaries contain masses of similar pigment. The liver cells are well preserved, as to form. The cytoplasm is very granular and a good many of the cells contain oil sacs of considerable size, but, as a rule, the integrity of the indi-

vidual cell is well preserved. The cell nuclei appear to be in a perfectly normal condition. Most of them contain one or more nucleoli.

Spleen.—The connective tissue elements of the spleen are increased. There is a large amount of deep greenish pigment scattered throughout the section, in every portion of the tissue. The lymph cells and leucocytes are, in many instances, heavily charged with this pigment. The vessels of the spleen show very little change, but, in places, the cells of the intima are apparently proliferating.

Pancreas.—The connective tissue, in the neighborhood of the larger vessels is increased in amount, but the nuclei of the connective tissue cells are neither prominent nor numerous and the increase seems to be chiefly confined to the subendothelial layer of the vessel walls. The interstitium of the gland, as a whole, can not be said to be greatly increased. The bodies of Langerhans are not numerous. The cells of the alveoli are large, regular in form, and their outlines, for the most part, are intact. The peripheral portion of the cells, down as far as the upper border of the nucleus, is quite clear, though it contains a few large granules. The intracellular network is plainly seen in this zone. On the contrary, the protoplasm of the base of the cells is filled with fine granular substance and this zone extends up to about the level of the centre of the cell-nuclei. Under the lower powers this division, into a clear and a granular zone, is quite striking.

Sub-Maxillary Gland.—Sections of this gland show no variation from the normal.

Kidneys.—The interstitial connective tissue is increased in amount, this increase being mostly marked about the vessels of the columns of Bertini and about the Malpighian bodies; it is almost exclusively limited to the connective tissue, surrounding and making up the walls of the blood vessels. The hyperplasia about the Malpighian tufts is evidently actively progressing. In a few vessels the cells of the intima are seen to be proliferating. The capillaries of the Malpighian bodies are evidently dilated and they are filled by blood cells; this condition does not pertain,

to so marked a degree, in the capillaries of other portions of the kidneys. The cells of the convoluted tubules are mostly intact, and they have fairly clear and regular outlines. The protoplasm of the cells of this portion of the kidney contains numerous large and highly refractive granules. The distal zone of these cells presents many clear spaces which are seen to be crossed by the intracellular network. The fatty degeneration, represented by these spaces, has been most extensive in this portion of the cells. The cells of the loop of Henle and of the straight and collecting tubules have a normal appearance for the greater part, but, occasionally, the protoplasm shows quite extensive granular change, except that the zonular arrangement is much less marked, than is the case in the cells of the convoluted tubules. The lumina of the tubules, of both cortex and medulla contain occasional hyaline casts and, nearly all of them, enclose masses of granular debris. The cell nuclei, in all parts of the organ, seem to be in a normal condition.

Ovaries.—The sections show no mature or immature Graafian follicles. Several corpora-lutea are present, all evidently quite old. The walls of the small vessels are thickened and several show quite marked increase of the subendothelial connective tissue coat.

Uterus.—The walls of the uterus show no microscopic changes of consequence. The glands of the mucous membrane show atrophic manifestations.

Lymph Nodes.—The retroperitoneal and mesenteric lymph nodes show no microscopic changes.

Blood Vessels.—Sections of the larger vessels show very little change, other than a fibrous thickening of their coats, but the smaller vessels, and the capillaries, frequently show proliferation of the endothelial cells of the intima. Hyperplasia, of the subendothelial connective tissue, is, as has been already noted, almost universal in the small vessels.

Peripheral Nerves.—The nerves of the cerebro-spinal system show a slight increase in the amount of endoneurium and perineurium, in some instances, but this change

is by no means constant. No other changes were found in the sections cut.

Muscles.—The voluntary muscles show occasional atrophic areas with interstitial increase. These changes are found most extreme, as already described, in the muscle of the tongue. No changes are present in the involuntary muscle fibres, save in the immediate region of some of the small arteries, where the interstitial increase has caused slight atrophy of some of the muscle bundles.

Bone.—Sections of the thickened walls of the calvarium show no variation from the structure of normal dense bone.

Brain and Spinal Cord.—A considerable number of fresh smears were made from various portions of the brain, as the central convolutions and the hippocampi; from the nuclei of the medulla; and from the spinal cord. The specimens were examined by Dr. Van Gieson; no morphological or cytological changes were found.

Semilunar Ganglia.—For the most part the ganglion cells stain in a perfectly normal way. The arrangement of the plaques is regular, and they react to the stain (Nissl) in a decisive manner. Occasionally, a cell is found in which the plaques have indistinctly reacted. Such instances are, however, rare. There is a considerable amount of pigment throughout the sections, and small masses of this substance are found in the ganglion cells themselves. There are no changes present in the connective tissue of the ganglia.

Superior Cervical Ganglia.—The cells of these ganglia react to the Nissl stain in an entirely normal manner. In the centre of some of the sections are found a few cells, whose plaques are but faintly stained; this is believed to be due to faulty permeation of the fixative, since sections from smaller blocks do not show this variation. There is a large deposit of light brown pigment both in the ganglion cells and scattered throughout all the sections. The endothelial cells, of some of the capillaries contained in the ganglia, are large and apparently dividing. No changes, quantitative or qualitative of the connective tissue of the

ganglia can be made out, except that, directly about the vessels, connective tissue hyperplasia is taking place.

Left Inferior Cervical Ganglion.—The ganglion cells stain in a normal manner. There is a small deposit of fine pigment in the ganglion cells, but none outside them in the surrounding tissue. The connective tissue cells of the ganglion, notably those of the perivascular connective tissue, are large and apparently proliferating in places; but the connective tissue increase is by no means marked.

Pneumogastric Nerves.—Cross sections of the pneumogastric nerves, which were hardened in osmic acid, show no degenerated fibres, nor any other change from the normal.

Cervical Sympathetic Nerves.—Sections of these nerves, taken both from above and below the inferior cervical ganglia, show no abnormalities in these trunks.

Adrenal Bodies.—No lesions are evident on microscopic examination.

Thyroid Gland.—Most of the alveoli contain more or less colloid substance. The epithelial cells, lining the aceni are regular and well formed, those of the alveoli, containing most colloid, are very much flattened, almost scale-like. A few of the smaller aceni are lined by two and even three layers of superimposed cells. The nuclei of the cells present no direct evidences of multiplication, though their chromatin elements stain very deeply.

Thymus Gland.—Examination of sections of the tissue, supposed to contain nodules of the thymus gland, shows them to be made up almost entirely of adipose tissue, in which are found patches of adenoid cells which contain an occasional indistinct Hassall's corpuscle and which are infiltrated by fat. No evidences of glandular hypertrophy are present, but, on the contrary, the picture seems to be one of degeneration and replacement of the thymus gland.

Pituitary Body.—The entire pituitary body is surrounded by a capsule made up, for the greater part, of highly vascular, loosely arranged, old, fibrous connective tissue. This capsule blends above, with the tissue of the infundibulum and posteriorly, with that

of the posterior lobe. The posterior lobe is seen, in cross section, as a half-moon shaped body, extending from above, where its tissue merges into that of the infundibulum, downward over two-thirds of the posterior aspect of the enlarged anterior lobe. Histologically, the structure of the posterior lobe of the hypophysis presents no variations from the normal; it merges into, and is continuous with, the tissue of the infundibulum. No traces of an infundibular ventricle are present. Just at the dividing line between the anterior and posterior lobes, are found a few large aceni, lined by flattened epithelial cells and filled by a colloid-appearing substance. These bodies are strikingly similar in their appearance to the colloid-containing alveoli of the normal thyroid gland. The remainder of the pituitary body is made up of the enlarged anterior lobe. This is divided into two distinct parts; an outer circular in form, embracing as a capsule a second portion, which is centrally located and distinctly mapped from the remainder of the anterior lobe. This last portion is described in the protocol, as the tumor body. Just beneath the investing capsule of the anterior lobe, are found large fibres of connective tissue arranged circularly, in cross section. Between these fibres are found single and double rows of epithelial cells, mostly cuboidal or flattened in shape, and pressed closely together by the surrounding connective tissue. Passing deeper into the section, the fibres of the connective tissue become smaller and more loosely arranged, and the cells between them assume, finally, the arrangement of glandular aceni, the size and shape of which vary greatly. There is considerable connective tissue stroma between the alveoli, portions of which are quite dense. This stroma carries numerous blood vessels, some of large size. The blood channels are mostly of the capillary type and are made up of but a single wall of endothelial cells, but the larger channels are surrounded by a small adventitia. Lymphatic channels are also numerous. The character of the cells which make up the glandular aceni varies considerably. Two varieties are easily distinguished, both by

their morphological and staining characteristics. The first variety, which is found to make up the majority of the alveoli, is columnar in shape, the nuclei are mostly situated near the base of the cells; the cell protoplasm is clear and stains a faint bluish tinge with hæmatoxylin and eosin. These cells are arranged in a single row, on a basement membrane, and the centre of the alveolus is marked by an open space, usually oval in shape. The second variety of cells are mostly ovoid in shape, larger than those just considered, and each contains a nucleus proportionately small, which is usually located somewhat eccentrically. The protoplasm of these cells is filled with large granules, which respond to the eosin in the hæmatoxylin eosin stain; to the indigo in Merkel's stain, and to the picric acid in the various differential stains which contain this ingredient. The arrangement of these cells is not constant. They are found singly, or in twos in alveoli, which are otherwise made up of the before-mentioned chief cells. In some cases they form an entire alveolus. Such alveoli are usually smaller than those made up of chief cells and owing to the shape and size of the former variety of cells, their arrangement in a single row is not very evident. Usually no distinct lumen of such an alveolus can be made out. These chromophilic cells are found in about the same relative number as in sections of the normal prehypophysis.

Surrounding the tumor, which, as stated in the protocol, is situated centrally in the cross section, is a condensation of connective tissue, forming a definite capsule of fairly dense fibres, about the substance of the tumor. This capsule contains numerous blood vessels, some of these are of considerable size and have well developed walls. Connective tissue fibres pass in from the capsule, carrying with them blood vessels and thus form the highly vascular connective tissue stroma of the tumor. The capsule divides the tissue of the tumor sharply from that of the anterior lobe, but posteriorly, in a few areas, the growth has broken through its capsule and has invaded the structure of the posterior lobe to a slight degree. The structure of the

tumor is simple and uniform. It is made up of columns of connective tissue, carrying thin walled vessels, limited by a thin basement membrane on either side, on which are arranged single rows of epithelial cells. These cellular columns are oval in cross section, for the most part, and they anastomose one with another in every direction. In the centre of each column, surrounded by connective tissue stroma, is found a thin walled vessel distended with blood cells. The cells are arranged on a basement membrane, as stated, for the greater part, but a few of them are found apparently independent of any surrounding structure. These are either columnar, or irregularly oval, in shape. A cell membrane is not evident. The protoplasm is extremely granular and these granules respond actively to the eosin, in the hæmatoxylin-eosin stain, to the indigo, of Merkel's stain, and, in general, exhibit uniformly the characteristic staining reactions of the chromophilic cell of the normal prehypophysis. Each cell contains a large nucleus of a fairly regular oval outline. A few of the larger cells contain two nuclei, the nucleus probably, having just divided. The chromatin elements of the nuclei have, in most instances, stained very deeply. Nearly all the nuclei contain one or more nucleoli.

This tumor is clearly adenomatous in nature, and, from the character of its cells, it has evidently originated from and, in general, follows, in its cellular structure, the type of the chromophilic, or granular, cell of the prehypophysis.

GENERAL CONSIDERATIONS.

This case presents several points of special interest in the consideration of acromegalia. In this instance the case seems to have represented but an early stage of the malady, judging from the changes in the external body. For this reason, the pathological studies are of special importance, since they would seemingly represent those changes which are found early in the development of acromegalia, and which are most essential in its production.

The absence of the frequent and severe neuralgic pains, which usually herald the approach of the disease, is interesting. The chief symptom, if we may be allowed to class it as a symptom, was the glycosuria and, indeed, the entire history alone as such, seems to be that of a case of simple diabetes mellitus; hence arises the very important question if diabetes is a symptomatic manifestation of the disease, a frequent accompanient of it; or, are both maladies brought about by one and the same cause? This point will be further considered under the pathology of the disease. The onset of the diabetes seems to have been sometime during 1896, and, probably at this time, referring to our photograph, the acromegalia was also already established. The death in coma, apparently of diabetic origin, is not uncommon in acromegalia.

The photograph of the patient, (Plate I, Fig. 2,) taken three years before death, shows a general facial aspect very suggestive of acromegalia, and it seems to the author that even at this time the disease had begun, but that the development was very slow up to within the last three months previous to her death.

The gynæcological symptoms, the malaise and the slight ocular disturbances are common manifestations of acromegalia. It is very probable that the pronounced glycosuria obscured many of the other common symptoms of the malady. The pruritus was, it seems probable, for the most part, due to the diabetes.

Pathologically, the point of greatest interest is the adenomatous growth of the prehypophysis. That this growth is made up entirely of cells of the chromophylic type, is a fact of the greatest significance, in considering the precise role which enlargement of the prehypophysis plays in acromegalia. The very extensive changes in the blood

vessels, especially the manifestations of capillary growth in so mild a case, is of great importance, as is also the active and general connective-tissue hyperplasia. The slight amount of osseous change would seem to indicate that, in at least some of the milder cases of acromegalia, bony changes are not as prominent as is usually thought to be the case.

Chapter III.

CASE III.

This case of acromegalia was first reported by Doctor Adler, in the *Medicinische Monatschrift*, some ten years ago. It was the first case reported from America, and Doctor Adler's paper was the fifth published on the disease.

For a history, the reader is referred to the original communication of Dr. Adler, and, since this gentleman proposes shortly to publish a study of the case, the author will entirely omit all clinical considerations and will utilize only the pathological findings, and their relations to acromegalia.

The patient contracted an acute nephritis which caused death early in the day, on November 19, 1898. The autopsy was performed by the author in the evening of the same day, in the presence of Doctors Adler, Sachs, Fraenkel, Onuf, and the house staff of the Montefiore Home. The author is indebted to Doctor Ales Hrdlicka for the careful anthropological measurements.

AUTOPSY.

The body is that of a gigantic female, it lies flat on the back. The left thigh and leg are everted, but are movable; the right thigh and leg are inverted at the same

angle as the left, but the hip joint is here partially anchylosed. The abdomen is protuberant, and the entire abdominal and thoracic mass is deviated one-third of its breadth to the left of the median line. There is an enormous bulging forward of the thoracic cage in the pectoral regions at the sides, and of the gladiolus in median line. The breasts are completely atrophic, and the nipples are almost obliterated; there is a faint pigmented area about them. Though the appearance of the thorax would indicate that the breasts were large, on palpation the breast tumors are found to be due entirely to the bulging of the thoracic cage in the mammary regions. The umbilicus is shallow and slit-like. The width of the pelvis between its crests 45.5 cm.

The neck is massive, the supra-sternal notch is full and plump. The attachments of the sterno-mastoid muscles are very prominent. The thyroid gland is much enlarged and easily palpable, beneath the borders of the sterno-cleidei.

The shoulder girdle is also massive; individually, however, the claviculæ are not particularly prominent. The shoulders are thrown forward and their great size appears to be principally due to the very large acromial and corcoid processes. The shoulders also project posteriorly, showing great enlargement of the scapulæ, especially of the spinous portions. As the body lies on the table flat on its back, the distance from spine of the 7th cervical vertebræ to a line parallel with the dorsal vertebræ shows an anterior kyphosis in the upper dorsal region of 14 cm.

The arms are large, and, in general, they are fairly symmetrical and well formed; the right arm is, however, somewhat larger than the left. On the contrary, the wrists are very large, so much so that they are decidedly out of proportion to the arms and forearms. The styloid processes and prominences are both enormously hypertrophied, and covered by osteophytes. The hands exhibit, in a most striking manner, the characteristic changes described by Marie. The fingers appear short and bulbous, as compared to the greatly enlarged hands. The thumbs are

rather less large, proportionately, than the fingers. The muscles of the carpus and digits are atrophied and the spaces are filled in by soft connective tissue growth.

The left thigh is somewhat larger than the right. The anterior tibial borders are rough. There is an old patch of cicatrix over the middle of the right tibia. The bones of the right leg are bowed outward in the median third. The feet are enormously enlarged, but not very greatly longitudinally, as the chief increase in size is in breadth and thickness; these proportions are simply startling. The toes are thick, and present the same bulbous appearance as the fingers. Here, as well as there, the nails are thin, broad, slightly curved and quite normal in appearance. The sole of the foot is found to be covered with great fleshy pads, that over the os calcis extending out posterior to the shank for a distance of 4 cm. On palpation the feet are found to be soft, but somewhat resistant. The bony enlargement in the feet is evidently of very much less degree than that of the soft tissues. There is a sharply circumscribed, somewhat indurated ulcer situated over the left great trochanter, it measures 3 x 2 cm.

The skin over the entire body is white and of a peculiar glistening, waxy, appearance. The epidermis is evidently thin, even over the soles of the feet and the palms of the hands; especially thin in proportion to the great thickening of the dermis, which is so hypertrophied as to give a very firm resistance, even elastic on palpation. There are a few pigmented moles on the skin of the upper thoracic region, and on the lower portion of the face.

There is some post-mortem lividity over the posterior surface of the body, but it is not extreme. The mons Veneris is small in proportion to the body, and is covered by a sparse growth of fine light brown hair. The left labium majus is much more hypertrophied than the right, which is but little larger than normal. Both labia show a peculiar brownish pigmentation, and the enlargement of the left labium is found to be of the connective tissue which gives a resistance entirely abnormal to these

cavernous structures. The clitoris is very large. It is covered by a heavy fold of mucous-membrane. The nymphæ are rather atrophied than otherwise. The fourchette is intact and carunculæ myrtiformes are found in the lower vagina. There is a putrid discharge escaping from the vaginal orifice.

There are two heavy folds in the skin extending across the abdomen, which show a slightly abraded epidermis at the bottom. A striking feature is that, notwithstanding the massive proportions of the body and general appearance of plumpness, there is a surprisingly small amount of subcutaneous adipose, if one may judge from palpation.

There are no abnormal areas of hair distribution. The hair of the head is thick, coarse, firmly inserted and dark brown in color, with a great preponderance of grey hairs. The hair extends down rather low on the neck. The hair of the eyebrows is sparse. The eyelashes are short and few in number.

Most striking of all is the appearance of the face. In general, it impresses one as being long and narrow. The inferior maxilla shows enormous prognathism, but it is fairly symmetrical in shape, though the right ramus and body is larger than the left. The teeth of the lower jaw project anterior to the superior dental arch for a distance of 3 cm. The malar prominences are large, more so on the right than on the left. The nose is enormous; the principal seat of hypertrophy is found in the cartilaginous portions, which are deflected towards the left. The end is nodular and very heavy. The alæ are thick. The nasal bones, which are covered by osteophytes, are also hypertrophied, though in a somewhat less degree than the cartilages. The orbital arches are much larger than normal. The zygomatic arches are also greatly enlarged, especially on the right. The ears are large, the left somewhat more so than the right, but their general form seems to be quite normal, though they are hypertrophied as a whole. The lips are thick, heavy and very firm. The mucous membranes are anæmic. The dentition is very poor and deficient. The teeth, for the greater part,

are only carious stumps. The alveolar arches are markedly hypertrophied. The tongue appears enormously enlarged. The left pupil is somewhat dilated, the right pupil is about normal. Both pupils are circular in outline. The skin of the face shows a great thickening of the dermis. There are several transverse furrows across the forehead, just below the prominent frontal eminences. As a whole, it may be said that the lines of facial expression are obliterated, and the features have a passive, immobile, rather melancholic appearance. The back of the head shows enormous hypertrophy of the occipital bone and of the mastoid processes.

The kyphosis of the spinal column, already mentioned, shows very markedly on the posterior surface of the body. The column is deviated in the upper dorsal region toward the left down as far as the lumbar portion, where it turns at a quite sharp angle back toward the median line. The spinous processes of the lower dorsal vertebræ are very prominent, and they are apparently covered by osteophytes. There is a circumscribed ulcerated surface, measuring 9 x 2 cm. on each buttock, the longest diameter of the ulcers being transverse to the body axis. A good many small, very vascular pigmented moles are found over the back. There is a clear serous fluid escaping from the nose and mouth. A soft yellow fæcal material is issuing from the rectum, which shows an extensively prolapsed mucous membrane.

Rigor mortis is pronounced and general.

SECTION.

Head.—The skull-cap is rather square in its general contour. The lines of suture are only partly united in places and are everywhere very distinct. The skull-cap shows areas, especially in the upper temporal region, where it is very thin, measuring no more than 1 mm. in thickness, while the central portions of bones, and of the frontal bone in particular, show large osseous nodosities. In the thin places, diploe is completely absent, but is

increased in the thickened areas which are almost osteoporotic. The largest nodes of thickening are situated as follows: on the left parietal bone 2.3 cm. behind the coronal and 2.4 cm. beneath the sagittal suture; on the frontal bone immediately in front of the coronal suture and to the right of the median line. As a whole, the calvarium is very light.

Cerebral Membranes.—The dura mater is thin; it shows a few small areas adherent to the pia over the vertex and over the temporo-sphenoidal lobe at the base. The pia mater is œdematous, closely adherent in places to the cortical substance, though the brain tissues are not lacerated when the membrane is torn away. It shows a moderate capillary congestion, which appears to be chiefly venous. There are calcareous plates along the falx cerebri. The superior longitudinal sinus contains a well-formed antemortem clot, which continues down to the torcular and laterally along the sinuses to their exit from the skull on either side.

Encephalon.—The entire brain is large. The cortical topography as a whole, appears to be fairly symmetrical. The occipital lobes, however, are somewhat flattened. The convolutions, generally, are ample, especially over the vertex, and the sulci are deep. The convolutions of the parietal regions are universally well developed, but somewhat less so in the frontal region. Both *optic nerves* and the posterior continuations are flattened and small, especially the portion corresponding to the left tract. No trace of a chiasm remains. A flattened mass of tissue 1 cm. square lies between the optic nerves at the point where the chiasm should be, but this is readily detached and does not seem to be connected with the nerves. The right nerve has a process 1 cm. in length and 2 mm. in diameter running off from its mesial surface nearly at right angles, toward the median line. The flattened right tract, in the region where the chiasm should be, is apparently amalgamated with the adjacent surface of the brain. The *infundibulum* is greatly enlarged; its ventricle widely

open. The tubercles on either side are unusually prominent. The *olfactory bulbs* are very large. Through the distended cavity of the infundibulum one can easily see the foramen of Munro, the anterior commissure and the anterior columns of the fornix. The *blood vessels* of the base show quite a general arterio-sclerosis, especially in the basilar artery, which contains several calcareous patches. The vertebral arteries on both sides show a spindle-shaped dilatation which is much more marked on the left side, where an almost saccular bulging of the wall is found. The intima of the vertebrals shows quite extensive arterio-sclerosis with calcification in plaques. Relative to the size of the *crura*, the *pons* appears small, especially on the right side. The *medulla* seems about normal in size in the upper portion, but the lower portion is hypertrophied to a size almost equal with the body; thus the medulla has the general form of a cylinder. The Sylvian arteries are large and show but slight gross change. The *cerebellum* shows an unusual heaping up of its substance to either side of the enlarged medulla, otherwise it exhibits no peculiarity.

Base of Skull.—The dura mater covering the base of the skull is unusually thick. The foramen magnum is elongated in its transverse diameter (2.7 cm.), which gives a flattened appearance in the antero-posterior direction (1.2 cm.). In its left wall is found a slight area of bony atrophy apparently due to pressure from the spindle-shaped dilatation of the left vertebral artery already mentioned. The entire base of the skull shows a robust marking of all the prominences, especially on the basilar process of the occipital bone, the petrous portions of the temporals, and on the floors of the temporal fossæ. The articulations of the occipital bone are bordered by a row of enormous osteophytes, but the bone in this region is not thickened; on the contrary, in places it is thinned down to 1 mm. in thickness. In such places, the diploë is almost wholly absent.

The *pituitary region* shows an extreme variation from the normal. The anterior cribriform plate is driven for-

ward and the olfactory grooves are shortened and deepened. The crista galli rises from between these grooves as a hypertrophied bony spine. The lateral boundaries of the sella turcica are all amplified. The dura in this region is, however, thickened so as to more or less obscure the precise bony structure. The posterior cribriform plate is broad and its posterior surface presents a ridge of distinct, ivory-hard osteophytes. The tubercles of the posterior cribriform plate are obliterated and the petrous ridges which lead to the plate on either side, hypertrophied and covered by osteophytes. Anteriorly, the tubercles are separated for a distance of 3.5 cm. The distance between anterior and posterior cribriform plates is 3.6 cm. The space thus defined is occupied by a fleshy mass which protrudes about 1.5 cm. above the level of the bony ring, is hemmed in by thickened membrane and is joined to the base of the brain above through the hypertrophied infundibulum. The carotid sinuses run directly through the sides of this mass. The tumor is well defined from the bony wall which it has correspondingly atrophied. A large vessel, apparently from the internal carotid, passes up from the base of the fossa near the right hand ridge into the substance of the tumor. Other vascular channels are also found leading to and from the mass. The carotid sinuses run on either side of the tumor, their walls fused with its substance.

The weight of the *pituitary tumor*, including the carotid sinuses on both sides, is 255½ grains. Sections through the pituitary body show that it is made up of a soft, bloody mass, which resembles, somewhat, the gross structure of the normal prehypophysis, excepting a less firm consistence and a much less abundant stroma. It measures in its greatest diameter, from before backwards, 3 cm., and from above downwards, 2.7 cm. It contains what appears to be a central cavity filled with a pultaceous bloody mass. That which presumably represents the posterior lobe of the pituitary body is a thin falciform layer just beneath the connective tissue capsule on the posterior superior surface of the tumor mass. On further exami-

nation the section presents soft areas of a yellowish color in contrast to firm, pinkish patches almost hyaline in appearance.

Thorax.—The *panniculus adiposus* is small in amount, bright yellow in color, and is made up, for the greater part, of thick areolar connective tissue infiltrated with fat cells. The muscles of the pectoral groups are firm and bright pink in color. The muscular volume is relatively quite small, but shows no gross abnormalities. The fat everywhere shows a large preponderance of fibrous elements.

The *costal cartilages* at their articulation with the ribs are somewhat enlarged, but not nearly as much so as in rachitis, though heaped up in a somewhat similar manner. These cartilages show considerable calcification. The *ribs* are unusually firm but not enlarged. The marrow of the ribs is particularly dry and the medulla is more than usually large in proportion to the size of these bones. There are dense old adhesions of both pleuræ, anteriorly. There is a considerable amount of light-colored fat on the interior surface of the anterior thoracic wall. The internal mammary arteries are very large, show thickened walls, and the lymph nodes along their course are enlarged and pigmented. The *sternum* is enormously hypertrophied in every direction and especially at the juncture of the gladiolus and manubrium. The depression of the manubrium at a sharp angle posteriorly from the line of axis of the gladiolus is very marked.

The *left pleural cavity* contains about one litre of seropurulent fluid. There are bands of dense old adhesions extending across this cavity. The *right pleura* is free laterally and posteriorly. Pleuro-pericardial adhesions are numerous and intimate.

Heart.—The *pericardium* is covered by a considerable quantity of light-colored fat. The sac is completely obliterated by dense old adhesions, which unite it to the epicardium over the entire surface of the heart. The *heart* is large, soft and flabby. The cardiac cavities contain small

ante-mortem clots on both sides. The heart walls are fairly thick, the muscle is soft, light in color, and shows an extreme interstitial overgrowth. The papillary muscles are, however, quite normal in appearance. The aortic and mitral segments are thickened and slightly sclerosed. The valves of the right heart show little change, and otherwise than the lesions mentioned, the endocardium is normal. The aortic arch is broad, though not particularly enlarged. The coronary arteries are large and show considerable endarteritis without calcification, a condition which is also present in the aortic arch, though in less degree. Weight of heart is approximately 19 oz.

Tongue.—The tongue is enormously enlarged, measuring from tip, to base of the epiglottis 18 cm., and across its broadest part, 7 cm. Its average thickness is 2.5 cm. The dorsum shows an enormous hypertrophy of the papillæ. The muscle which makes up the body of the tongue is soft, flaccid, very light in color and apparently the fibres are atrophied. The papillary layer of connective tissue appears to be enormously thickened.

Tonsils.—The tonsils are slightly enlarged, but the lymph nodes on the posterior surface of the tongue are relatively still more hypertrophied.

Thymus.—There are no evidences of a persisting thymus gland.

Thyroid.—The thyroid gland is enlarged to about four times its normal volume. The colloid follicles are numerous and large, but otherwise nothing abnormal is seen on gross examination.

Œsophagus.—The œsophagus shows no abnormality.

Lymph Nodes.—The cervical lymph nodes are enlarged and, in places, quite markedly anthracotic. A few contain fibroid or calcareous nodules, the origin of which is not apparent.

Cervical Nerves.—The trunks of the *pneumogastric nerves* are greatly enlarged. In their entire course on both sides of the neck the *sympathetic trunks* are hypertrophied to about four times their normal size. The *carotid arteries* show an enormous degree of sub endothelial endarteritis.

Respiratory Tract.—The *epiglottis* is small and pointed. The larynx does not appear to be enlarged. The lumina of the *trachea and large bronchi* are about normal, their mucous membrane shows chronic congestion. The *lung tissue* generally is emphysematous, but the lower lobes are congested and show a moderate interstitial increase. The bronchial lymph nodes are enlarged and extremely anthracotic. The left lung shows patches of atelectasis, posteriorly.

Liver.—The right lobe of the liver is enormously enlarged; the left lobe, if changed at all, is atrophied. The capsule of the liver is thickened. The tissue is firm, and shows a congested interstitium with the lobules marked in light yellow. The connective tissue is apparently considerably increased, especially about the interlobular vessels. Weight of liver is approximately six pounds. The *gall bladder* is distended and contains about 15 cm. of light golden bile. The duct is patent.

Spleen.—The spleen is greatly enlarged, measuring 22.5 cm. in length and 13 cm. in breadth. The capsule is thickened, the cut surface is under tension and scrapes with ease. The splenic tissue shows great connective tissue increase, extreme congestion and the structure, to the unaided eye, is completely obliterated.

Digestive Tract.—The *stomach* is dilated. It contains a considerable amount of partly digested food. The mucous membrane is congested but otherwise seems to be normal.

The intestinal coils are distended with gas. The *intestine* as a whole appears to be markedly hypertrophied. The *caput coli* is greatly dilated, measuring 30 cm. in circumference. The mucous membrane of the large intestine shows no abnormality except that the solitary follicles are unusually numerous. The *mesentery* is long and thick.

The *appendix* measures 13 cm. in length. It is invested by a complete mesentery and shows no pathological change besides hypertrophy. The *mesenteric lymph nodes* are enlarged and apparently there is an interstitial increase.

The *pancreas* is greatly enlarged; the tissue is firm and light pink in color. The pancreatic artery is dilated to about three times its usual size. The connective tissue of the pancreas is greatly increased.

Adrenal Bodies.—The adrenal bodies are hypertrophied to about four times their ordinary volume. The tissue is extremely vascular. Both cortex and medulla are proportionately enlarged. On gross examination, nothing of significance is discovered in the left body, but the right contains a large area of recent infarction.

Urinary Organs.—The *kidneys* are greatly increased in size. The left kidney measures 19 cm. in length, and 9 cm. in breadth. The right kidney is 16 cm. long and 10 cm. broad. The general conformation is natural and symmetrical. The capsules are congested, and quite adherent not only to the cortex but also to the surrounding tissues. The markings are indistinct. The cortex, which is comparatively thin, is mottled with small hemorrhagic areas and extensive yellowish patches. The perivascular connective tissue is enormously increased in quantity. There are numerous small hemorrhages in the pelves of both kidneys. It is important to note that while the connective tissue elements are perhaps most increased, there is also an actual hyperplasia of the secreting portions of the organs. Approximate weight of kidneys is two pounds each. The *ureters* are large but otherwise present no change. The *bladder* is much enlarged and contains about one litre of turbid, light-colored urine. The mucous membrane is greatly congested.

Internal Genitals.—The *uterus* is very small, measuring 5 cm. in length, while the fundus is 4 cm. in breadth. The cervix is patulous. The uterine mucous membrane is atrophied and somewhat congested, otherwise normal. The *ovaries* show extreme atrophy. The *tubes* are normal with the exception that the left shows hydrops of its fimbriated extremity.

Lymphatics.—The abdominal lymph channels, including the receptaculum chyli, are very large; they show no other apparent abnormality. The mesenteric and retroperi-

toneal lymph nodes are increased in size and some are deeply pigmented.

Sympathetic Nerves.—The sympathetic *trunks* and the *ganglia* of both the thorax and abdomen are greatly enlarged.

Aorta.—The abdominal aorta is of normal size. Just above the bifurcation the circumference is 3.5 cm.; at the level of the diaphragm it is 2 cm. The intima shows a considerable thickening, with sclerosis in plaques.

Back and Spinal Column.—There is a marked scoliosis to the left of the dorsal *spinal column* and a kyphosis, as mentioned in the external examination. The *muscles* of the back are atrophied, soft and light pink in color. Fatty infiltration is slight. The spinous processes of the *vertebræ* show numerous osteophytic projections. The *spinal canal* is greatly enlarged throughout its entire course.

Cord and Peripheral Nerves.—The *spinal cord* terminates at the level of twelfth dorsal vertebra. The dura mater spinalis shows numerous plaques of bony thickening; they are in largest number in the mid-dorsal region, and some of them are so large that they nearly surround the cord. Similar plaques, but not as large, are found in the pia mater. The spinal cord, in the cervical region, is larger than normal. It measures 1.7 cm. in its largest diameter; the dorsal portion of the cord is not enlarged. The spinal cord is firm and presents no gross lesion. The *peripheral nerves* are, for the greater part, enlarged; their texture is unusually firm, apparently due to an increase in the endoneurium.

Skeleton.—The greater part of the skeleton was removed at the time of the autopsy, and as it is proposed as the subject of a subsequent anthropological study, only the chief or general lesions of the osseous system are mentioned here.

In general, the shaft bones are elongated, the growth obviously having taken place, at least in greatest degree, at the ends of the bones. The seats of muscular, tendinous, or fascial attachment are universally hypertrophied

and covered by numerous, ivory-hard osteophytes. The shafts of the bones are not hypertrophied, but, on the contrary, are in places very evidently atrophied, so that the circumference, notably that of the long bones, is below the normal for an individual of this stature. The bones were found to be of light weight and, on maceration, considerable difficulty was experienced, as even in a weak alkali they were almost disintegrated. Aside from the osteophytic projections, the bulk of the bony structures are of a very porous character. The marrow of the bones is unusually dry and the cancellous spaces of the medullary portions are very large. Notwithstanding the great elongation and apparent hypertrophy of the inferior maxilla, when denuded of its soft structures the bone itself was found fragile and atrophied.

The changes in the skull have already been sufficiently mentioned for our present purpose.

Notwithstanding the mammoth proportions of the subject and the splanchnomegalia, it is most interesting to note that the weight, taken but shortly before death, was less than 150 pounds.

MEASUREMENTS.

Diam. ant. post. max.	20.8	cm.
Hair line occp. max.	20.0	cm.
Diam. lat. max.	15.8	cm.
Height of head from interauricular line.	9.7	cm.
Diam. biauricular	14.8	cm.
" front. min.	9.9	cm.
" bizyg. max.	14.9	cm.
" bigon	12.6	cm.
Chin to hair line	23.6	cm.
" to interciliary line	17.7	cm.
" to nasion	17.0	cm.
Separation of external canthi	10.4	cm.
" internal canthi	3.75	cm.
Nasion: to base of nose	7.3	cm.
" to tip of nose	7.6	cm.
Width of nose	4.6	cm.
" of mouth	5.6	cm.
Height of left ear	8.0	cm.

Width of left ear		4.7	cm.
Circumference of neck		40.4	cm.
"	of chest at the level of nipples	122.0	cm.
"	at level of umbilicus	112.0	cm.
Umbilicus to sternal notch		40.5	cm.
Circumference of upper arm (left at middle)		29.5	cm.
"	forearm, max.	28.7	cm.
"	wrist, min.	21.7	cm.
"	of thigh, max.	63.7	cm.
"	at middle of thigh	46.5	cm.
"	of knee joint, max.	44.2	cm.
"	leg, max.	34.7	cm.
"	leg, min.	26.8	cm.
Left hand:	Wrist line to base of medius (internally),	10.8	cm.
	Internal length of medius	8.5	cm.
	Width of palm at middle	10.9	cm.
Left foot:	Max. length	27.1	cm.
	Max. width (about 7 cm. post. to the base of toes)	11.8	cm.
	Width of heel at middle	8.8	cm.
Fingers and toes:	Left medius, outside length	12.4	cm.
	Length of first bend	7.2	cm.
	" of second bend	4.6	cm.
	" of third bend	3.1	cm.
	Circumference of middle of first phalanx	9.0	cm.
	Circumference of second phalanx,	7.8	cm.
	Circumference of third phalanx,	6.8	cm.
	(Tape applied without pressure).		
Left thumb:	Ex. length of first bend	5.0	cm.
	Ex. length of second bend	4.1	cm.
	Circumference over middle of first phalanx	8.9	cm.
	Circumference over middle of second phalanx	7.7	cm.
Left great toe:	Internal length	4.35	cm.
	Circumference max.	10.7	cm.

As the tissues were removed from the body they were immediately placed in fixing fluids, of which formol, alcohol, Müller's fluid and Zenker's mixture were mostly used. As soon as the specimens became sufficiently hardened, they were embedded in paraffin and cut.

MICROSCOPIC EXAMINATION.

Skin—(*from over right calf*).—The epithelial layer, as a whole, is of about the usual thickness, but the stratum corneum is deeper than is ordinarily found in this region. The epithelial cells show no evidences of active proliferation. The dermis is greatly thickened and made up of a dense felting of white fibrous and yellow elastic fibres; this marked connective tissue thickening extends deep down into the sub-dermal adipose tissue. Cellular elements are few in number. The dermis contains a surprisingly large number of sweat glands of large size. The lumen of the larger ones is lined by stratified cuboidal epithelium. The dermis is very vascular, especially the papillæ, but the vessels are markedly small and their walls are much thickened. The nerve trunks of the skin show an increase of both endoneurium and perineurium. The skin covering the hypertrophied ear shows similar conditions.

Scalp.—The epidermis is thin, especially the stratum corneum. The dermis shows the same thickening, already noted in the skin, and the small amount of fat beneath the scalp shows an unusually large number of fibrous elements; the elastic fibres are rather more abundant here than in the skin. The hairs are deeply inserted and show nothing abnormal, either in stalk or follicle. Sebaceous, and especially sweat glands, are very numerous. The sections do not show blood vessels in unusually large numbers; those present have a fibrous thickening of their walls.

Voluntary Muscle—(*Right Soleus*).—The endomysium and the perimysium show a moderate increase in volume and their cellular elements are numerous and large, apparently proliferating. The size of the muscle fibres varies from small to large; cross striation is well marked, and the areas of Cohnheim are very plainly seen in cross section. The nuclei of the muscle fibres are frequently found in almost continuous rows of from three to six or, less often,

in smaller groups. In some cases, where the myoplasm is much degenerated, the resulting space is occupied by a mass of nuclei. Mitotic figures are not uncommon in these muscle nuclei. A few small blood vessels in the endomysium show endothelial cells which are apparently proliferating.

Bone—(*hypertrophied end of rib*).—The compact bone shows nothing unnatural in its structure; the medullary portions show unusually large cancellous spaces. The medulla has a very great blood supply but contains very little fat. Numerous multinuclear giant cells are arranged along the borders of the compact septa extending deep into the medullary substance; apparently a destruction of the compact tissue is taking place with an extension of the medulla.

Cartilage—(*costal cartilage*).—The perichondrium is thick; the chondrogenetic layer does not, however, show unusual cell proliferation. The cellular elements in the cartilage itself are extremely numerous, the lacunæ being closely placed and, for the greater part, containing more than one cartilage cell, some enclosing as many as six. A good many of the lacunæ have calcified walls. The matrix is also quite extensively calcified in areas. The elastic cartilage from the helix of the right ear is also highly cellular. It shows no apparent variation qualitative or quantitative of the fibrous elements, and the increase in size is, in all probability, due to actual growth of the cartilage.

Blood.—Unfortunately no determination of hæmoglobin or blood cell counts were made shortly before death. This defect has been supplied as far as possible by examination of the blood post-mortem, although of course this procedure is not reliable.

The red corpuscles are fairly regular in outline and size. Poikilocytosis, in a moderate degree, is, however, present. The staining reactions of the red blood cells are such as would indicate a low percentage of hæmoglobin. Neither nucleated red cells nor any pathological form of the erythrocyte are present. The leucocytes

appear to be relatively increased in number; their relative percentage is as follows:

Polynuclears.....	74 per cent.
Lymphocytes.....	18 per cent.
Mononuclears.....	5 per cent.
Eosinophiles.....	1 per cent.
Transitionals.....	1 per cent.

Heart.—The muscle cells of the heart are large. Cross striation is well shown in nearly all the cells. The nuclei are normally situated and are fairly regular in shape. A good many of the cells present the ordinary brown pigment at the poles of the nucleus, except that it is coarser than usual. The sarcoplasm of a few cells is granular, but, as a rule, they are quite natural in appearance. The interstitial tissue of the heart-muscle is very considerably augmented, though evidences of recent proliferation are wholly wanting. The universal fibrous thickening, so frequently mentioned, is seen in the vessels.

Wall of Aorta (Thoracic).—The wall is, as a whole, thickened. There is a considerable increase of the sub-endothelial connective tissue, but it is not general, being found only in isolated areas. The entire endothelial coat is even and unbroken. The internal fenestrated membrane is not differentiated from the mass of elastic fibres which make up the bulk of the wall of the artery. The wall contains only a very small amount of muscle fibres and the thickening seems to be due to an increase in the fibro-elastic elements. The vasa vasorum are numerous but normal in appearance.

Left Carotid Artery.—The obstructive endarteritis, mentioned in the protocol, is found to be almost entirely limited to the sub-endothelial layer of connective tissue, which shows a very great increase of its elements. Evidences of an active process are, however, absent. The remaining walls of the vessel seem to be in a normal condition.

Left Vertebral Artery (*Sacculated Area*).—The endothelial layer is intact. The sub-endothelial connective tissue is increased to about the thickness of all the other coats of the artery together; it is highly cellular but does not appear to be actively proliferating. The internal elastic membrane is thick, and presents no break of integrity. The media shows extensive changes; the muscle cells are few in number and widely separated by an intimate growth of connective tissue fibres. A good many of the muscle cells show evidences of protoplasmic degeneration. The adventitia of the vessel is somewhat thickened. Vasa vasorum are numerous and normal.

Left Sylvian Artery.—As in the case of the vertebral artery this vessel shows the characteristic lesions of an obliterating endarteritis of moderate degree involving all three coats equally.

Lymph Nodes.—The nodes of the thoracic, cervical and abdominal systems show the same set of changes. These glands present a simple hyperplasia of their normal elements, the fibrous tissues being proportionately most increased. The glands are particularly rich in connective tissue cells. The adenoid cells do not show any direct proof of recent active growth. The nodes contain a good deal of pigment, both in the cells and in the stroma. The blood vessels of the glands are numerous and are generally filled with blood cells. Their walls are universally thickened.

Spleen.—The capsule and all the connective tissue elements of the organ show a marked overgrowth. Connective tissue cells are especially numerous. The proliferation has been most extensive about the vessels. The amount of pigment is very small. The lymph-adenoid cells of the spleen show no abnormality, either in themselves or in their arrangement.

Lung.—A good many of the air sacs are considerably distended and some have ruptured into the neighboring spaces. A few air sacs contain an exudate of leucocytes

with a small fibrin meshwork. Desquamation of the epithelium of the alveolar walls is quite extensive. Connective tissue increase is not apparent in the sections examined, except about the larger vessels. Sections from the lower lobes show less emphysema, but here many of the air spaces are filled by a bloody exudate and the vessels are universally congested.

Tongue.—The epithelium, which covers the papillæ of the tongue, is not more than ordinarily thick. The papillæ are, however, very much larger than normal, their tops are squared, blunt, and the upper strata of the epithelium contain but few keratoid cells. The filiform papillæ are hardly to be distinguished from the fungiform, both being of the same general shape and the latter variety but slightly broader than the former. The nuclei of the epithelial cells show no evidences of rapid reproduction. Prickle cells are unusually well shown everywhere. The connective tissue, which makes up the body of the papillæ, is very much increased, and mainly accounts for this increased size. Secondary elevations are present on both filiform and fungiform papillæ. The sub-epithelial connective tissue is quite highly cellular, and very vascular. There is considerable infiltration of this tissue by lymph adenoid cells. The muscle fibres of the tongue show extensive atrophic changes of the same nature as those already given in the skeletal muscles, but of much greater degree and at the same time the endomysium is much more over-developed. The vessels and nerve trunks show here the general connective tissue hyperplasia.

Liver.—The interlobular connective tissue septa are markedly thickened, as is the case with the visceral connective tissues generally. The increase is in both white and yellow elastic fibrils, and is of an adult form of the tissue. There is a considerable small round-celled infiltration about the interlobular structures. The vessels of both the portal and hepatic systems have thickened walls with a surrounding abnormal connective tissue growth. The portal capillaries are widely distended and irregularly

congested. The liver cells are apparently somewhat smaller than ordinary, their outlines are distinct, regular, and contain from one to three nuclei. The protoplasm is very granular in most of the cells, a considerable number show quite extensive pigmentation. The bile capillaries are normal in their appearance.

Pancreas.—The connective tissue stroma of the pancreas is much thickened, the increase being an adult form of areolar tissue. An interstitial growth extends into the acini and even between the cells themselves. The lobules are compressed, and atrophied evidently from pressure. The cells are small and very closely arranged, but they show no abnormality of cytoplasm or nucleus. Bodies of Langerhans are very scarce.

Kidneys.—The connective tissue framework is increased everywhere, but no areas of active growth are seen. The increase is most extreme about the blood vessels, especially the Malpighian bodies. Though this hyperplastic connective tissue is in an adult form, no contraction or cirrhosis has yet taken place. The blood vessels, both in the cortex and medulla, are extremely congested, and in the former, diapedesis of the white blood cells is quite prominent. Many of the convoluted tubules contain granular debris and a few well-formed granular casts. Hyaline casts are quite abundant. The cells of the convoluted tubules are, in places, completely desquamated. Although, for the greater part, the tubules are still lined by cells, the majority of the latter are broken down and project into the lumen in irregular masses. The nuclei of these cells are intact, but the protoplasm is extremely granular and many cells are almost entirely eroded, leaving the nuclei quite or nearly free. Fatty infiltration is present in a few cells. In the cortex are found several tubules completely filled by cells, the cytoplasm of which is very much less granular than that of the ordinary renal cells; evidently these are resting cells or, perhaps, newly developed. The collecting tubules show no abnormality. Though the interstitial tissue is much augmented in the kidneys, this alone is insufficient to

account for the mammoth size of these organs, the hypertrophy of which is therefore partly dependent on an actual reproduction of the normal renal parenchyma.

Ovary.—The layer of germinal epithelium which covers the ovary is thin, the cells flattened and in places entirely wanting. The cortex is made up entirely of a dense but highly cellular connective tissue and contains no Graafian follicles. A few scars are found in some of the sections which evidently mark the site of old ruptured follicles. The medulla is made up of a still more dense and less cellular connective tissue. The vessels are few in number for this organ, closely contracted, and some are obliterated by endarteritis.

Uterus.—The uterine wall contains only a small amount of muscle, but is chiefly made up of a highly cellular fibrous connective tissue. The muscle cells, where found, are small, thin, and contain but a small amount of cytoplasm. The uterine sinuses are small; they contain blood cells, among which are leucocytes in relatively large number. Everywhere the walls of the vessels are thickened by a growth of connective tissue. The mucous membrane contains but few glands, having apparently been replaced by the overgrown connective tissue. Where glands are present, they are small and lined by imperfectly formed cells. The innermost zone of the mucosa is very granular and almost necrotic.

Brain—(Left precentral lobule).—Many of the blood vessels show a fibrous thickening of their walls. The nuclei of the endothelial cells of the intima are often large and distinct but display no karyomitotic figures. Nothing abnormal is apparent in the neuroglia. About some of the capillaries are a good many leucocytes which have wandered out of the vessels into the surrounding tissue. The ganglion cells, as a rule, stain normally and show the Nissl plaques in a natural state. A few cells are found which do not give a typical reaction to the Nissl blue, but there are none which show a complete degeneration of the plaques or any morphological destruction of the

cell. A great many of the cells show the nucleus wandered toward the side of the cell body, and, in such instances, the nucleolus usually exhibits a corresponding transition with reference to the nuclear membrane.*

Spinal Cord.—(*Sixth cervical segment*). All of the membranes of the cord show a fibrous thickening and, in places, deposits of lime salts. In both gray and white matter the perivascular connective tissue is much increased and is of the adult form. This connective tissue increase also involves the anterior fissure and posterior septum. Although the connective tissue increase is quite exclusively perivascular, yet taken collectively it seems sufficient to account for the increased volume of the cord in this region. The neuroglia of the gray matter seems to be normal. The ganglion cells of the anterior horns respond to the Nissl stain in a natural manner and all the cells are morphologically perfect, but, in the posterior horns, a few cells are found which show a partial degeneration of their plaques. Pigmentary changes are wholly absent. In the tracts of the cord occasional fibres are found which are degenerated; these are most numerous in the posterior columns. The dorsal segment shows exactly the same conditions as the cervical cord, with the exception that the connective tissue overgrowth is very much less extensive and degenerative changes in the ganglion cells of the posterior horns are rather more pronounced.

Right Gasserian Ganglion.—The connective tissue of the ganglion and its nerve bundles is increased, both in white fibrous and yellow elastic elements; the cells are large, numerous, but show no mitotic figures. The ganglion cells seem to be in a normal condition; they react naturally to the Nissl stain.

Peripheral Nerves.—Sections of many of the enlarged trunks of the peripheral nerves show, in each case, the same picture—an unusually pronounced endoneurium and

* Van Gieson has stated that this movement of the nucleus toward the periphery of the cell takes place when the cell nutrition is deficient and that it precedes cell degeneration, of which it is often the first indication.

perineurium. The connective tissue, in each instance, is in adult form and the cellular elements are few. Many of the trunks contain degenerated fibres.

Sympathetic Ganglia.—The enlarged left inferior cervical ganglion, which, together with its trunks was macroscopically very much enlarged, when sectioned, showed the greater number of its cells normal; a few showed the milder forms of degeneration in which the plaques reacted poorly, while some contained a few pigment granules. The amount of connective tissue in all the sympathetic ganglia is much above the normal.

The majority of the cells of the cœliac ganglia are normal, but various degrees of degeneration are also found, from slight cytolysis to actual cytoclasis. A good many of the more degenerated cells contain considerable pigment. The abnormal size of the ganglia is, no doubt, entirely dependent on connective tissue hyperplasia.

Sympathetic Trunks.—In the protocol, it was mentioned that the sympathetic trunks, and notably the cervical cords, were much larger than usual. Microscopically this enlargement is found to be entirely due to an over-production of connective tissue. This process is of such extent as to seriously compromise the nerve fibres of the trunks and a good many of them are found degenerated.

Adrenal Body.—The adrenal tissue is entirely normal except in the infarcted region. This region is mostly made up of a necrotic, blood infiltrated tissue, in which all traces of adrenal structure have been wiped out. Where the blood clot has been partly absorbed, the fibrous framework of the gland exhibits evidences of proliferation. Leucocytes charged with pigment, and occasional free nuclei of adrenal cells, are found in such places. Where the destruction is less, acini of adrenal cells are found which still retain their form, but, in nearly all cases, the cytoplasm shows advanced degenerative alterations or is replaced by large oil globules. Both the cortex and medulla of the gland are involved in the infarction. None of the sections show reconstructive changes on the part of

the adrenal cells. The entire area of infarction is apparently of comparatively recent origin, probably not more than five or ten days' standing.

Thyroid Gland.—Microscopically, the thyroid gland shows nothing abnormal. The colloid-containing acini are perhaps rather more numerous and large than is generally the case, but the substance of this secretion reacts in the usual manner to the ordinary staining reagents. Resting acini are few in number. None of the cell nuclei show mitotic figures, nor are there any other evidences of unusual activity.

Pituitary Body.—In general, the structure in all parts of the sections is similar. The entire mass is surrounded by a capsule of dense adult connective tissue. This membrane varies in thickness from .05 mm. to 2 mm. It contains numerous thick-walled blood vessels, which are mostly filled with blood cells. Some of these vessels show hyaline degeneration of their walls. Occasional medullated nerve trunks and non-medullated fibres are also found in the capsule. In places, the capsule is quite largely composed of yellow elastic fibres though white fibrous tissue predominates. This capsule is invaded, in many places, by the cells of the underlying tissue. A loose connective tissue stroma passes in from the investing membrane, and divides the cortical zones of the mass into distinct lobules and acini; toward the centre this arrangement becomes less and less apparent so that very little stroma is seen here, excepting in thick sections, and the alveolar formation is difficult to identify. In a few places there are masses or whorls of connective tissue of considerable size which exhibit a variety of hyaline degeneration and usually enclose a centrally situated blood vessel. The connective tissue network carries numerous thin-walled blood vessels, many of which are filled with blood cells. Even where the stroma is in very small amount, blood vessels are numerous. The connective tissue of the stroma is not highly cellular, but, on the contrary, is almost exclusively fibrous. The small blood channels are, for the greater part, simple endothelial tubes, but

frequently in those areas nearest the posterior lobe, a few smooth muscle cells are disposed along their walls. There are numerous extravasations of blood cells in patches varying in size from a few microns to several millimetres. Some of these are sufficient to almost obscure the structure of the tissue. Some of the capillaries seem to empty directly into these spaces. A large area of this character occupies the centre of the hypertrophied pituitary body, and is described in the protocol as "a cavity containing a pultaceous, bloody material." In none of the sections are there lesions which could be said to be of an inflammatory nature, and not even where invasion of the capsule has taken place is there to be seen any surrounding inflammatory reaction.

The cellular elements in the outer zones of the growth are arranged in little groups or acini, surrounded by connective tissue. In the centre of the mass this same arrangement persists, but is much less apparent, except in thick sections (10 to 15 microns). The cells have the same character in all parts of the growth, and are of two distinct varieties. The first variety, the least numerous, is more frequently found in the peripheral portions where the acinous arrangement is most evident. These cells are all mononuclear, small and oval, or low columnar in form, and when located on the basement membrane formed by the stroma, the nucleus is situated near the attached base. The protoplasm is but slightly granular or quite homogeneous in appearance. The nuclei show the chromatin elements very distinctly but no evidences of mitosis are present. It will be seen at once that these cells resemble almost absolutely the chief cells of the normal prehypophysis.

The second variety of cells composes the bulk of the tissue in all parts of the structure. These cells are very irregular in their arrangement to the stroma. They fill up the centre of the acini, are also found free, infiltrating the capsule and making up the walls of the blood spaces. The size varies from approximately twice to three times the diameter of the red blood corpuscle. When isolated,

the cells are ovoid or spherical, but when closely grouped, the shape is modified by pressure. The protoplasm is devoid of a cell membrane and often has a jagged appearance or blends with its neighboring cells. The cytoplasm is very coarsely granular, and reacts decidedly to eosin and picric acid in their various staining combinations. Some cells contain large open spaces and still others, fine, brown pigment granules. In the hemorrhagic areas, several cells are found which enclose in their protoplasm fragments of, or even entire red blood corpuscles, hence it seems that these cells possess, at least to some degree, the power of phagocytosis. The cells contain from one to four nuclei; a few only have more than two; the majority are mononuclear. The centrally situated nucleus is usually spherical. Its size varies considerably, being largest in the mononuclear cell. The nucleus is also smaller and more ovoid in those cells containing two nuclei and usually small, irregular in form, and surrounded by but a thin ring of cytoplasm in the polynuclear cells. Nearly all the nuclei contain one or more nucleoli. The chromatin skein in the larger nuclei is loose and particularly rich in granules. No karyokinetic figures are seen, though in the polynuclear cells the arrangement of the chromatic fibrils occasionally resembles defective mitoses. This variety of cell is very evidently identical with, or derived from, the chromophilic cells of the normal hypophysis.

The sections contain several colloid areas, which are found most plentifully in the regions adjacent to the posterior lobe. The acini of this colloid formation are lined by chromophilic cells, but frequently their cytoplasm is found merging into the colloid mass, leaving the cell nucleus almost free. Diffuse patches of colloid substance are also found, containing broken down chromophilic cells, their substance so blending with the colloid masses as to leave but little doubt that this material is formed from or by these cells. In several of these colloid patches, the cell disintegration has been so complete that the nucleus itself is found partly degenerated, and surrounded by the completely metamorphosed

cytoplasm alone. Scattered diffusely throughout all the sections is a coarse, granular substance which is similar in its appearance and staining reactions to the granules of the chromophilic cytoplasm.

The posterior lobe of the pituitary body shows quite an extensive infiltration in its inner zone by the cells of the enlarged anterior lobe. The vessels of the posterior lobe show considerable fibrous thickening of their walls, which, in places, exhibit hyaline degeneration. There is a large deposit of fine, brownish pigment throughout the posterior lobe. A few degenerated forms of nerve cells are still clearly apparent. The cellular elements of the connective tissue in the posterior lobe are very numerous and large, and occasionally their nuclei show pictures which resemble karyokinetic figures. In general, however, the structure of the neural lobe is very close to the normal.

GENERAL OBSERVATIONS.

The above case is of particular interest since, in a most characteristic manner, it presents the picture of fully developed, quiescent acromegalia.

Clinically, the disease had made no progress in the last few years, indeed very little change seems to have taken place since the time when it was first put on record by Doctor Adler. The deformities had not increased and we are entirely justified in looking on the case as one which had long since advanced to a terminal stage.

The atrophy of many of the bones and the general osteoporosis are among the most unusual and extraordinary lesions presented by the case. The changes in the bones, we have every reason to believe, followed on an osseous hypertrophy, just as we have seen that in this disease true muscular atrophy often follows hypertrophy.

The general connective tissue hyperplasia, mentioned so often, is a constant feature of the disease and one of its most significant lesions. In this case, however, the

condition differs from that in Cases I and II, in that here the hyperplastic connective tissue is seen in an *adult* form, while in the other two cases it was universally in a state of *active proliferation.* This fact would again lead us to think that the disease process had reached its terminal stage and no longer responded actively to the proximate causative factors, or that these factors themselves had ceased to act, or were greatly diminished in intensity.

The tumor of the pituitary body is undoubtedly an hyperplastic or adenomatous enlargement, originating in, and simulating in general structure and arrangement, the anterior lobe. The growth has been almost entirely of the chromophilic cells and in this respect resembles the chromophilic adenoma found in Case II. The general appearance of the tumor, and especially its cellular characteristics, lead one to conclude that it is *no longer an actively proliferating structure, but that it represents at this period a degenerative stage.* This surmise is borne out by the extensive cell degeneration present and more especially by the irregular nuclear multiplication seen in the polynuclear cells.

GENERAL DISCUSSION OF ACROMEGALIA.

Chapter IV.

HISTORICAL REVIEW.

Acromegalia, as a morbid identity, was first described in 1886 by Pierre Marie while chief assistant at Charcot's clinic. In his original paper, Marie uses as the basis of his studies two cases then in the wards of Charcot at the Salpêtrière; he also reviews several cases described by previous authors under various names, as gigantism,

myxœdema, hypertrophy of the tongue, etc., showing their close correspondence to this newly identified condition which, from the very characteristic enlargement of the extremities, he had named *acromegalia* (ἄκρον) end, (μέγας) large. That the disease, in itself, was by no means new, is proven by these cases and by others, collected from the older medical publications of various writers. From the literature extending back as far as 1552, Sternberg has brought together several undoubted cases. Some of these reports give very accurate pictures of the disease as we now know it. The majority of such cases is found reported under gigantism, and allied headings. Examinations of the skeletons, especially of the skulls of giants, have demonstrated that many of them show anomalies which we now believe to be typical of acromegalia. In a study of gigantism, published in 1872, Carl von Langer divided the cases into two classes. The characteristics of one of these are almost typical of the acromegalic. No doubt a close study of the literature of the various trophic disorders will place many of these obscure cases under the probable head of acromegalia.

In 1884, Fritsche and Klebs described a very characteristic case of the then unknown disease, and Fritsche collected several similar cases, which, as he states, give "*Ein wohl charakteristisches Krankheitsbild.*" Klebs, at the same time, reported a like case under the diagnosis of gigantism. Broca followed Marie's original article by a report in which he described the bony changes found at the autopsy on one of the cases first recorded by Marie.

In 1887, Klebs produced a study of the disease under the title of "*Ueber Akromegalie* (*Krankhaften Riesenwuchs.*)"

in which he reviewed and discussed, both from a pathological and clinical standpoint, eleven well marked cases.

In 1888, Marie published a more complete study of acromegalia with an especially important consideration of the pathology. In 1889, he contributed to *Brain* an article, in which he calls attention to hypertrophy of the pituitary body, persistence of the thymus gland, and to hypertrophy of the cord and ganglia of the sympathetic system, conditions which are usually found at autopsy in cases of acromegalia. Marie states that he believes these lesions to be constant in the disease and characteristic of it.

Meanwhile, Adler, Godlee, Strümpel and Dercum reported, with excellent studies, several cases.

In the same year in which Marie's last article was written, appeared a most excellent monograph on acromegalia by Souza-Leite, a pupil of Marie. This work completely reviewed the previous studies of the disease and made many important additions to our knowledge of it. He collected 48 cases in his final report which probably included every authentic case reported up to that date.

In the early part of 1893, Collins completed an exhaustive critical review of all the cases of the disease published up to that time. In this review he reported a series of 83 cases, and in a brief yet thorough manner considered their symptomatology and pathology.

J. Arnold has also published a tabular review of similar nature, but with a somewhat fuller discussion of the pathology.

From 1886, the date of Marie's first publication, up to the present time, many papers have been written on the subject of acromegalia and numerous cases have been reported; only a few of the most important studies are mentioned above.

Among the papers of special merit, must be mentioned those of Virchow, Dana, Hutchinson, Boyce and Beadles, and Strümpel, and particularly the recent publications of Tamburini and of Sternberg. To the most excellent monograph of the latter, the author is especially indebted for much of the material which has been utilized in the preparation of this paper. Indeed it would be impossible, after so complete and systematic a study had been written, to say anything of the history and general pathology of acromegalia without repeating much that has already been said by this distinguished and thorough investigator.

The name *acromegalia*, which was applied by Marie in his initial work, is manifestly inappropriate, since it refers to only one of the important indications of the disease, viz.: the enlarged extremities, which, it must be remembered, are also found, though in less degree, in other diseases; and the name does not cover the more important changes found in the face, or those pathological lesions which we now know to be extremely characteristic. Verstraten and others have chosen the name of *Marie's disease;* and, though it be but just that this distinguished clinician should receive full credit for his work, it seems unfortunate to designate a disease by any other term than one which will, to a greater or less degree, describe the main characteristics of its symptomatology, or better, pathology. The name *pachyacria* which has been proposed by Von Recklinghausen, seems to best fulfil these conditions, meaning, as it does, general thickening, thus expressing very clearly the general pathological condition found in the disease. Marie has advanced the term *akromakrie* as a fit name, but it seems less appropriate than that of *pachyacria*. Notwithstanding the fact that acromegalia is universally

acknowledged to be far from a suitable name, it is very improbable that any other term will come into general use, since the condition has now become so well known by this designation.

Chapter V.

ETIOLOGY.

Concerning the etiology, or predisposing causes of acromegalia, it may be briefly stated that nothing is known. Heredity appears to play no part, since it is only in very occasional cases that hereditary influences, either direct or indirect, can be found. Exceptions, however, exist; a notable one is given in the brothers Hagner, reported by Friedrich as cases of general hyperostosis. Syphilis has been, no doubt, most frequently assigned as one of the etiological factors (Schmidt, Smirnoff) but we know that it is more often absent and in many cases its presence is given as only possible, while the pathological findings, as in Case I, do not indicate the presence of that disease. Very likely the lowered general condition induced by syphilis may, however, predispose to it. Alcoholism has also been mentioned (Ghirlenzini), but on account of the very general prevalence of the alcoholic habit, it is difficult to find a case in which alcohol may not have been a factor. However, in an experience extending over three years in the alcoholic wards of Bellevue Hospital, where the alcoholic service is probably the largest in the world, not one case of acromegalia has yet been seen. The infective diseases have been mentioned as possible factors, and no doubt they have preceded and perhaps favored the development of the disease, as in the case mentioned by Souza-Leite, but this is by no means

constant. Rheumatism and gout have been named, without apparent proof of their influence (Souza-Leite). The pathology of the disease, in so far as is yet known, would not tend to establish any of these as productive agents.

Cases have been reported that developed after a severe fright. We know that the very closely allied condition of Basedow's disease is often apparently brought on by fright; but from the cases yet reported, we can barely conceive it more than a coincidence in the etiology of these special cases of acromegalia. This seems, however, to be one of the most probable of the etiological factors commonly mentioned. (Pel, Naunyn, Schleisenger, Hanseman). A case recently reported by Furnival, coming on after a railroad accident, should perhaps be classed under this head. The menopause has been given as among the predisposing causes, but is now generally thought to be a result of the disease and not a productive agent. It is well to note here, that in males also the genital functions become less active as the disease becomes established. No doubt any condition which lowers the natural resistance of the body, or which tends to produce abnormal overgrowth, may act as an aid to the development of the disease. Nevertheless, it can as yet be safely said that the etiological factors of acromegalia are entirely unknown.

COURSE.

The disease attacks both sexes in about equal number.

It is found among all races—Indian (*Dana*), Negro, (*Berkeley*), Mongolian, (*Ogata*, *Matignon*). All classes and conditions of people are subject to the disease, though naturally the larger number of cases are reported from among the middle classes. Now that the condition is so

well recognized, its occurrence appears less rare and exceptional. In the city of New York alone, the author has within the past year (1897-98), found eight well-marked cases, including the three reported in this paper.

The condition is frequently found associated with other forms of chronic disease as syringomyelia (Baruch), and tabes (Nonne). It is most frequently reported as accompanying diabetes mellitus, but, as will be shown later on, glycosuria is so frequently present in acromegalia, that it is generally believed to be one of the symptoms of the disease. The facial neuralgias reported are clearly symptomatic, as are also the various ocular complications which will be mentioned further on. The gigantism, so frequently found associated with acromegalia, is probably a part and parcel of the disease itself, (Langer, Klebs, Dana, Hutchinson, Walters and others), though by no means are all giants acromegalics.

Acromegalia generally develops between the years of nine and twenty-six (Souza-Leite); several instances of its onset before puberty are published. Walters reports a case in which the disease was well established at the thirteenth year. Cenua cites a case of acromegalia which he believes to have been congenital and it has been known to come on after the sixtieth year (Dercum). It seems best to note here that the development of the disease during childhood is not credited by Marie.

The duration of acromegalia is uncertain, ranging from three to thirty years. Death usually results from some intercurrent affection grafted upon an organism weakened by the long-standing general disease. Death in diabetic coma is a very common termination in those cases in which glycosuria is a prominent symptom. (See Case II).

SYMPTOMATOLOGY.

So perfect is the description of the disease, as given by Marie in his original study, that very little can be added.

The onset is so slow that it often happens that the patient is wholly unaware of his abnormal condition. He has usually noticed that, for some time past, the size of his hats, shoes and gloves, has constantly increased; again, the first note taken of the change may be from comparison of a recent photograph with one taken some time before. Frequently the deformity is first remarked by his friends who have been absent for some time. As a general thing, the patient has made very few complaints. Perhaps he has had occasional neuralgic pains over the distribution of the trifacial nerve; he may have noted that he is not quite as strong as the usually large body and musculature would indicate, but the voracious appetite is likely to throw both him and his friends off their guard. He may complain of cold and of wandering pains in the extremities. The increase in size of the head, hands and feet is almost always the first physical change observed. At about this stage the friends of the patient usually remark that he begins to stoop somewhat; and, although the general appearance of the patient is such as would indicate great power and strength, he may be found to be below the average. At an early period of the disease the muscular strength may increase to above normal, a subsequent diminution rapidly taking place (Hutchinson). The movements of the patient usually become somewhat slow, and quick muscular acts are very imperfectly done. Sexual desire dwindles, and in the female, menstrual irregularities begin to develop; the

menses may appear at regular intervals, but the flow may be decreased in quantity or even sometimes increased; usually, the menses, though previously regular, come on at irregular intervals and the quantity of blood passed decreases. In general, the symptoms of the approaching menopause develop, and these, in many cases, still further delude the female patient into the belief that all the symptoms of the disease are accounted for by the oncoming "change of life."

The mental condition in the earlier stages shows, very few changes; as a rule the patients are quiet and, though apathetic, are often of a cheerful temperament rather than otherwise. Ideation is slow, but the patient is usually able to attend to his ordinary business and social duties. Somnolence, however, becomes more and more marked as the disease progresses. It is a noteworthy fact, however that somnolence is most marked in those cases which show glycosuria as one of the symptoms. Not uncommonly, apparently from constantly brooding over their changed appearance, the patients become melancholic. Cases complicated with various mental disorders, as hysteria, (Guinon), or insanity, (Pick, Berkeley, Tanzi), are reported. The writer has recently seen a case in which melancholia was a pronounced symptom. Anamnesic aphasia is not uncommon (Rathmell).

Sleep is usually rather deeper than ordinary, and more is required. In the average case, as all these symptoms become more marked, the patient begins to complain of headache, neuralgic pains over the trifacial distribution, and of a sense of fullness in the head; frequently, too, there is more or less transitory disturbance of vision; polyuria often develops and becomes more and more troublesome, and perspiration may also be abundant. A physician is finally

called, either for some intercurrent affection, or more generally, on account of the neuralgias, polyuria or the genital irregularities. Even when the disease is but slightly developed, the general appearance of the patient, with the more or less constant presence of the above symptoms, at once attracts the attention of the careful clinician and arouses in him strong suspicions of what gradually and finally becomes the very striking picture of well-developed acromegalia. In certain cases, the disease appears to be arrested at some period in its development and in a few doubtful cases the changes already present appear to retrograde. However, such instances are very rare and in the ordinary case, the changes become more and more apparent, with greater or less rapidity, but with fatal certainty, until the patient presents the well-marked characteristics of the disease.

Chapter VI.

PHYSICAL SIGNS.

When the disease has become well advanced, the physical variations are so characteristic and many of them so constant that it is necessary to note them in detail.

Marie has described two types of the *acromegalic hand;* the first is most common and also most characteristic. (Plate II, Fig. 2). The hand as a whole is enlarged, but the enlargement is proportionately much less in length, so that the general appearance is stumpy and spade-like. The *fingers*, though of usual length, give one the impression of being short; they are considerably increased in circumference, the ends are bluntly rounded. The dorso-palmar diameter of the digit is increased, so that the cross-section of the finger is rounder than

in the normal hand, thus giving to the fingers the classic "sausage shape." The increase in the volume of the fingers, though partly bony, is, for the most part, of the soft tissues. The folds of the fingers, and all the places of fascial attachment are deeply marked. The nails are short, usually somewhat flattened and thin. The pulp of the finger generally projects beyond the free margin of the nail for a considerable distance. The changes are about equally marked in all the digits, but those in the thumb are frequently most apparent. The alignment of the fingers is usually stated as normal, but in those cases that we have studied, the fingers have been spread apart, and the thumb especially, has been deflected outward as though the circumference of the base of the digits was so great as to prevent their close and linear approximation. When the fingers are extended, the dorsum is thrown into heavy folds, as though the tissues covering it were too abundant. The metatarsal depressions are obliterated, and the muscles and tendons, as a rule, are not to be made out.

The palm of the hand is much thickened. This change is chiefly of the soft structures, though the bones of the metacarpus are more or less enlarged and sometimes show osteophytic projections. The fleshy parts of the palms are so much hypertrophied and the palmar lines so deep, that when the digits are partly flexed, the surface of the hand is thrown into thick, fleshy, cushion-like folds. The hollow of the hand is usually obliterated and the thenar and hypothenar eminences are marked by large soft protuberances. The thickening of the hand is most extreme in the metacarpal region; and the skin here may be somewhat cyanosed. The palms are often covered with beads of perspiration. The movements of the hands

are slow and clumsy, but in most cases, the sensation appears to be normal. The grasp is usually diminished.

The second type of acromegalic hand, described by Marie, is less characteristic. The enlargement is more symmetrical and the hand more normal in general contour; the increase in length as well as the breadth being proportionate. In short, the hand is well formed but gigantic. It must be remembered, as Sternberg has pointed out, that the changes in the hand in some cases of acromegalia are so slight as to be indefinite, a fact which must always be emphasized in the diagnosis of doubtful cases.

Usually the *wrist* is enlarged; this enlargement is chiefly bony and most marked in the distal extremities of the radius and ulna. The shafts of the forearms are symmetrical and present little to attract the attention; but when compared with the enormous spade-like hands, they seem even smaller than they really are. The muscles of the forearm are not prominent; frequently they are atrophied, and soft and flabby to the touch. The muscular reactions, however, are usually normal. Generally, the elbow joints are enlarged and present osteophytic projections.

The external and internal condyles of the humerus are especially prominent. The muscles of the arms are, in many cases, atrophied; the circumference of the arm is strikingly disproportionate to the enlarged elbow and massive shoulder. The shoulder girdle is very broad, principally due, as will be shown later, to the great enlargement of the clavicles. The acromion processes overhang. The musculature of the shoulder joint usually appears small in proportion to the massive bony outlines.

Changes similar to those of the upper extremities are found in the *lower extremities*, and these are most marked

in the feet. Briefly the *acromegalic foot* presents the same characteristics as the hand. It is, as a whole, voluminous. The toes are cylindrical, and give the impression of being shorter than normal; but measurements have proven this to be only apparent. The great toe generally shows the most pronounced abnormalities. It is frequently deflected from the median line of the foot and, in typical instances, its volume is enormously increased; the nails are broad, short, smooth and thin. The plantar arch is very often defective, so that many patients show a typical flat foot. The fleshy pads of the plantar surface, like those of the palm of the hand, are hypertrophied and the intervening folds are deep. The dorsal surface of the foot frequently presents an œdematous-like puffiness; this does not pit on pressure, as in œdema, but is firm and solid to the touch. The base of the third phalanx of the great and small toe and the distal extremities of the corresponding metacarpal bones often show very marked enlargement. The heel is usually much enlarged and its inferior surface is covered by a great fleshy pad. It is often found to extend out far back of the tibio-astragaloid articulation, as is the case in the negro. Probably the descent of the plantar arch giving rise to flat foot is also a factor producing the retroversion of the heel as well as the enlargement of the heel itself. The ankle joint is enlarged, but the shaft of the *leg* is small, and exhibits that same relative disproportion to the size of the foot that exists in the upper extremities between the forearm and hand. The muscles of the calf are frequently somewhat atrophied. The knee in most cases is very prominent and bony hypertrophy, especially of the patella, is very marked. The *thighs* show perhaps the least change of any portion of the extremities. The mus-

cular volume, however, is in general somewhat less than one would expect from the size and length of the body.

The changes present in the face are very characteristic and they are the most constant external evidences of the disease. The *head*, as a whole, is enlarged, but this increase is seen to be most marked in the face, the contour of which becomes an elongated oval (Plate I, Fig. 1). The most striking changes in the face are found in the jaws and especially in the lower jaw; this member shows a greater or less degree of prognathism, in nearly every case. The entire jaw is increased in size, giving to it a "lantern jaw" appearance, but the enlargement is most evident at the symphysis. The superior maxilla is also prominent and enlarged, though to a somewhat less degree. The alveolar processes are hypertrophic and the teeth, which in themselves, show no variation from the normal, are widely separated. The tongue is greatly increased in size, not only in thickness but especially in its lateral diameter and the borders show teeth marks. The top is usually squared. The filiform and fungiform papillæ, on the dorsum, are very prominent. The movements of the tongue show no apparent change. The lips are thick and the mucous membrane, especially of the lower lip, is everted, and as a rule, the corners of the mouth are drawn down. The nose almost invariably presents a very characteristic picture; as a whole, it is enlarged, but the most noticeable abnormalities are of the lower portion. The end of the nose is large and globular, presenting occasionally a well marked central sulcus; the alæ nasi are thick and heavy, and the anterior nasal passages are widely distended; the latero-nasal folds are heavy, but not distinctly defined. The malar prominences are greatly exaggerated. Both superior and

inferior orbital ridges are enlarged, but the superior usually overhangs the inferior, and the fold of skin forming the eyebrow projects over in a large fold. The eyelids are thick and heavy; the eyelashes are generally normal. The eyeballs vary greatly in their appearance; in some cases they present no noticeable change; in other cases, as stated by Dercum, they may show exophthalmus, or may be deeply seated in the orbital cavity so that they appear small. The pupils frequently present irregularities, and paralyses of various ocular muscles have been observed (Plate I, Fig. 1). In some cases, the forehead, especially the frontal eminences, are prominent, but in the vast majority the forehead is retreating—an appearance which is heightened by the heavy over-hanging eyebrows and the greatly enlarged face. The ears, as a rule, show more or less hypertrophy, but in most cases this seems to be fairly symmetrical and to follow the anatomical type present in the individual before the onset of the disease. The distribution and quality of hair on the head and face present no peculiarities. The general impression of the face is massive. The emotions produce little change of features, the face usually bearing a stolid, passive, emotionless, and, as a rule, somewhat melancholic expression.

The *neck* varies between short and long extremes, but is always thick and heavy; perhaps, most commonly, it is relatively short and deeply set between the shoulders. Often an enlarged thyroid cartilage and gland is apparent and sometimes the lower portion of the neck is also abnormally full and prominent, due to persistence or enlargement of the thymus gland.

The *thorax* presents many points of interest. The thoracic cage as a whole is enlarged. Its transverse and

antero-posterior diameters are most increased, while the length of the chest is proportionately short. The sternum is thrown forward, the gladiolus generally projecting outward from the angle of the manubrium. Posteriorly, the capacity of the respiratory chamber is increased by an antero-posterior curvature of the spinal column. Thus the cervical portion of the column is generally thrown forward and the dorsal portion backward, producing a double curvature and giving the peculiar stoop-shouldered appearance usually seen in acromegalics. The chest, in its entirety, has somewhat the appearance of the emphysematous thorax, with the exception that the base is proportionately larger.

Changes in the *pelvis* are not very constant, except that the anterior spines and the cristæ are hypertrophied. Sometimes the depth of the pelvis is increased and in some cases, the inter-spinous measurement is augmented. The pubes are often very prominent. In general the pelvic changes are neither constant nor characteristic.

The lower dorsal and lumbar portions of the *spinal column* frequently present a greater or less degree of lordosis; lateral deviations of the spinal column are also present.

The *abdomen* is generally full and more or less pendant; but seen in comparison with the enlarged thoracic cage, it often appears retracted, especially in its upper zone.

The *body, as a whole*, is often greatly enlarged, presenting truly gigantic proportions. Twenty per cent of the cases cited by Sternberg, are stated by this author to be of the gigantic type. The author has recently seen a well-marked case exhibited as a giantess by one of the large show companies. Dana, Massalongo, and others, have collected several similar cases, and we may in

reality look on giantism as one of the evidences of acromegalia.

The *skin* of the body as already stated, is thickened in certain areas, as on the hands and feet, over the face and shoulders, or, in general, over those parts which exhibit the most characteristic changes of the disease.

In nearly all cases the *external genitals* show changes; in women the labia are hypertrophied, and often the clitoris is considerably enlarged. In men, notwithstanding the diminution of sexual desire and activity, we usually find hypertrophy of the penis and in some cases the testicles are also enlarged (Dercum); but we must remember that not infrequently atrophy of all these organs is reported.

One side of the body often shows changes of greater degree than the other. Usually in these cases, it is the right side which is most involved (Osborne).

The *movements* of the body are slow and clumsy, due probably to muscular atrophy and to the unwieldy extremities. The gait is slow and cumbersome, the feet being slowly dragged over the ground; as a rule the hip and pelvic movements are exaggerated. *Vocalization* is impaired, especially of those words containing syllables which demand use of the tongue. The voice often becomes deep and heavy, consequent upon the hypertrophied larynx and the thickened vocal cords.

The *posture* of the body is more or less characteristic; the head and neck are thrown forward, the shoulders are bent and protruding; the abdomen is pendant and the legs are held somewhat widely apart, while the enormous feet are usually everted.

Notwithstanding the many evidences of muscular insufficiency, both nerve and muscle *electrical reactions* are usually normal.

The *pulse* is generally full but, in well advanced cases, soft and more or less irregular, though it may be perfectly normal (Lithauer).

The respiratory system reveals but little abnormality, usually emphysema (Schwartz) and a greater or less degree of bronchitis (Appleyard, Gerhardt, Bamberger).

Examination of the *urine*, in those cases suffering from polyuria, often reveals the presence of considerable quantities of sugar (Strümpel, Cunningham, Burg), though in some of these cases, the urine is typical of diabetes insipidis (Pick, Graham, Schwartz). Casts of various kinds are often present with albumenuria (Thompson, Osborne, Packard). Often the urine is normal (Surmont, Ruttle, Strembo).

Chapter VII.

PATHOLOGICAL ANATOMY.

It will be quite essential in this chapter to reconsider many of the physical signs in order to determine their relation to the lesions in the various tissues. This repetition is especially necessary in the detailed description of the patho-anatomical changes of the osseous system.

Skin and Appendages.—The pathological changes in the skin develop early in the progress of the disease. They are, as one would naturally expect, greatest in the integument covering those parts which we have already noted, as most extensively enlarged, *i. e.*, over the hands, feet, face, neck and shoulders. Macroscopically the skin in these areas is considerably thickened; the surface is rough and often fissured. A general brownish pigmentation is present in the average case, which, at times, strongly resembles that found in Addison's disease.

In still other cases, as in one which the author has recently seen, this skin pigmentation is a dark olive green color. In certain cases, instead of being general, the pigmentation is confined to localized areas.

Fibroma molluscum are frequently found distributed over various parts of the skin, perhaps most generally on the face, (Marie, Souza-Leite, Paget, Massalongo and others). Dermal papilloma are also present in many cases, and these are most commonly found on those parts which show greatest deformity. Microscopically, the *epidermis* does not show very constant changes; it is sometimes considerably thickened, and, at other times, not at all. Where cell proliferation is found, it is naturally most marked in the stratum Malpighii though also present in the stratum granulosum, where the pigmented cells are often greatly increased, or, as is frequently the case, the amount of pigment in the lower stratum of the rete Malpighii is much augmented. The most constant changes are found in the *corium;* here, in almost every instance where the examination has been recorded, variations of great importance have been found. The papillæ are increased in number and size. This change is most marked in the palms of the hands and the soles of the feet; papillæ of the compound variety are often unusually numerous in these regions. The connective tissue, making up the bulk of the corium, is usually hypertrophied to a considerable degree and the connective tissue cells of this region show active proliferation. The capillaries and small arteries here are very numerous and often widely dilated. Mitosis of the endothelium of the intima of these channels is often evident. The *sweat and sebaceous glands* are frequently multiplied, especially in their ordinary areas of distribution. In well marked cases of the disease, these

changes in the corium are quite constant, so that thickening of this layer is evident, even on superficial examination.

This connective tissue increase, we must note, seems to be but a localized manifestation of the *general connective tissue hyperplasia*, which, as will be demonstrated further on, is the *characteristic pathological process* of the disease.

In many of those cases marked by glycosuria, boils are frequently found and eczematous areas about the genitalia are common. Where the perspiration is greatly augmented, the superficial epithelia becomes more or less macerated by the acid secretion. However, these changes can hardly be mentioned as those of acromegalia itself, but are rather secondary manifestations of primary symptoms.

Changes in the *hair*, quantitative or qualitative, are neither constant nor characteristic. In many cases the hair is thick and luxurious while in other cases fine and sparse. The hair of the face of female acromegalics, in certain instances, becomes coarse and abundant, as in a case recently reported by Bailey, in which a quite distinct beard was present. In males, however, the beard is often thin and fine. As Sternberg has said, this may be due, in both sexes, to the diminished sexual activity of the patient. In several cases a falling out of the hair is recorded; such an instance is cited by Dodgson. No doubt, in at least some of these cases, the alopecia is a result of specific disease.

Osseous System.—The most striking of all the lesions in acromegalia are found in the bones, and changes in the bony framework are usually among the first manifestations of the disease which become apparent to the patient and to his friends. The increased stature, the

enlargement of the head and of the extremities, are in part, directly dependent upon the increased volume of the bones underlying the soft tissues.

Head.—As we find some of the most characteristic external manifestations of the disease shown in the head and face, so do we find that the bones of the skull, especially those of the face, present some of the most striking of the lesions. As might be expected, the general type of the skull, in itself, varies with that presented by the subject before the disease has become established. Perhaps the most striking feature, and that which first attracts the attention to the head, is the massive and protruding *lower jaw*, and indeed this is, as already stated, recognized as one of the chief diagnostic points of the disease. The rami of the lower jaw-bone are not greatly changed in themselves, nevertheless the whole bone is usually enlarged. The variations from the ordinary are most pronounced in the body of the bone, which juts sharply forward and which is often enormously enlarged so that it appears heavy and cumbersome. The symphysis often projects forward and all the outlines of the bone are found to be exaggerated. The condyles are enlarged and the glenoid cavities of the temporal bones are deeply hollowed, so that both the lateral and antero-posterior excursions of the jaw are wide. The seats of muscular attachment and insertion are all hypertrophied and the grooves are deeply cut. Although all the natural ridges and tubercles are accentuated, abnormal tuberosities are not commonly found on the lower jaw. In consequence of the marked prognathism, the teeth of the inferior alveolar arch are carried out beyond those of the superior arch. Notwithstanding this, the angle at which the teeth are inserted usually remains about normal. The alveolar arch is

generally considerably hypertrophied and the teeth are inserted into it at widely separated intervals. Often the bone of the hypertrophied arch is of a somewhat spongy character, so that the teeth in such cases are loosely set. The teeth of both the upper and lower jaws ordinarily show no unusual structural changes.

Although the abnormalities of the inferior maxilla are so very striking, those of the *upper jaw* are scarcely less so, but from the character and position of the bone these abnormalities are rather less evident. As in the lower jaw, the alveolar processes are thickened and enlarged, the teeth of the superior arch show the same width or variety of spacing. The most constant abnormality found in the upper jaw is, no doubt, the great increase in size of the antrum of Highmore which bulges forward the anterior plate, often almost completely obliterating the fossa, normally so distinct beneath the inferior orbital ridge. It is partly this deformity which gives to the face that puffy and œdematous look commonly seen in acromegalia. The muscular attachments of the bone, both of its anterior and posterior aspect, are accentuated and enlarged. The infraorbital foramina are large and, in some cases, surrounded by raised bony rings.

The *malar bones* are heavy and greatly exaggerated in every dimension, giving rise to the prominence of the malar region already mentioned. The *zygomatic arches* are thickened and, though the enlargement is symmetrical, they are rough, covered with ridges and particularly massive in appearance. The entire orbital ring shows this same hypertrophied growth which is extended to the nasal bones. All areas of muscular attachment show prominent and over-rugged ridges and fossæ, while in places, the foramina for the exit of

nerves and vessels, are encroached upon by this bony overgrowth.

The *mastoid* and *styloid processes* show, to a very marked degree, the same general change and, as has already been stated, the glenoid fossæ of the temporal bones are broadened and rendered shallow.

The entire *calvarium* in a large per cent of typical cases is universally enlarged and its walls are often increased to two and three times their usual thickness. The frontal sinuses, as well as the antra of Highmore, are augmented, so assisting, together with the hypertrophied superciliary ridges, in giving the heavy beetled brow, sometimes seen. The temporal ridges are roughened and heavy. As a rule, all the sutures are thoroughly united, but their line of union is rough and irregular. Posteriorly, the entire occipital bone is often found hypertrophied to such a degree as to outstrip, in its abnormalities, its enlarged fellows which make up the remainder of the cranial vault. The occipital process may jut sharply outward and even be the seat of secondary tuberosities and roughness. Both the superior and inferior curved lines are much exaggerated and rough; indeed, on the bones of the calvarium, as has been already said of the bones of the face, every muscular attachment is prominent and roughened. At the *base of the skull* the changes are perhaps less striking but here also, as one would expect, we find almost universal hypertrophy of the various processes.

The *interior of the skull* presents several anomalies. The walls of the cranium may be greatly thickened, but we must not fail to recollect that, in certain cases, they have been found perfectly normal in this respect. As the skull-cap is removed, the depressions and grooves for the reception of the venous sinuses appear broadened

and deeply sunk into the internal plate of the bone. The grooves of the meningeal arteries are deep and frequently their edges are sharp. The fossæ of the base of the skull are deep and the deepened depressions for the vascular channels, noted in the calvarium, are also present.

Of the various lesions of the interior of the skull, however, the most remarkable are the alterations in the centre of the cranial base,—changes confined to the sphenoid bone, or in the more extreme cases, including also the bones adjacent to the *pituitary fossa.* (Plate V, Fig. 1). This depression is formed and its extent increased, in every direction, at the expense of the surrounding bony walls. Cases are on record in which the fossa has been so hollowed out by the tumor growing within, that the base of the bone was completely removed and the fleshy mass occupying the space was found projecting down into the posterior pharynx. The olivary process has, in the greater number of cases, become obliterated, so that the space encroaches on the optic groove, and the anterior clinoid processes are found elevated, thinned and pressed upon. Laterally the base of the sella turcica may be hollowed down to a level with the floors of the cavernous grooves. Posteriorly, the dorsum Ephippii is found very thin, sometimes perforated or completely divided, by the constant pressure exerted upon it by the hypertrophied pituitary body. In a certain number of cases this plate exhibits a curvature backward and then forward; in such instances it is continued up and over the surface of the tumor, so being considerably elongated. In those cases where the tumor seems to have grown in a more upward direction the upper portion has undergone a pressure absorption, which sometimes has resulted in complete obliteration of the

upper portion of the plate, including the middle and posterior clinoid processes. The walls of this greatly enlarged pituitary fossa are frequently thin and fragile; the bony limitations may be completely eroded through, so that the mass contained within the fossa rests in the body of the sphenoid bone; and even this is, in some cases, necrosed. It will be noticed that all the changes in this region mentioned thus far, are directly dependent upon an enormous increase in size of the pituitary body. In the few doubtful cases, where enlargement of the pituitary body was not found, these changes in and around the sella turcica were not present.

But additional deformities are still found in the *sphenoid bone ;* from the pressure constantly exerted by the growing mass on the anterior clinoid processes, the optic foramina become pressed upon by the processes and, from the same cause, the space of the foramen lacerum anterior, is encroached upon by the hypertrophied lesser wings of the sphenoid. The inner surface of the greater wings of the sphenoid are roughened and hypertrophic, so that the foramina for the exit of the branches of the fifth nerve are more or less narrowed. The presence of abnormal tuberosities has been noted in a few cases, but ordinarily they are not present.

Abnormalities of the *temporal bone* are not general, but in some cases the tumor growth has been sufficient to encroach on the apex of the petrous portion, causing more or less absorption of it, and consequent pressure on the foramen lacerum medius.

The *basilar process* of the occipital bone exhibits, in some cases, a hollowing out of its superior surface. This abnormality is probably present in those cases in which, as reported by Virchow, the medulla is hypertrophied.

Vertebral Column.—The lesions of the spinal column result in various abnormal curvatures. An antero-posterior curvature involving the cervical and upper dorsal regions, is perhaps most common. Lateral curvatures, however, are by no means infrequent, and a lumbar lordosis, possibly of a compensatory nature, is very common. These curvatures seem to be dependent on abnormalities of formation or growth in the bodies of the vertebræ, for we find that in the lower cervical and dorsal region, the anterior portion of the bodies is thinner than the posterior. The bodies of the vertebræ usually, however, show increased volume, so that the diameters are augmented in every axis, but some vertebræ are found, as reported by Brigidi, in which the bodies are thinned and apparently undergoing absorption. In extreme cases where the kyphosis has constantly increased, more or less bony absorption of the bodies must take place. The sides of the vertebral bodies, especially in those parts of the spine which show most deformity, are rough and the points of ligamentous attachment are exaggerated, while the upper and lower borders as well as the sides, may show numerous exostoses. The internal structure of the bodies is somewhat less firm than normal. The *laminæ transversæ*, and especially the *spinous processes* of the vertebræ, being points of muscular attachment, show marked hypertrophy and thickening; exostoses are numerous and large in these areas. Often the spine of the vertebra prominens is unusually prominent.

Thorax.—The *sternum* shows quite characteristic changes as would be expected from the deformity of the chest. The angles of the ventral surface of the bone are exaggerated so that the juncture of the manubrium with the gladiolus is at an obtuse angle while the axis of the

gladiolus is deflected forward and downward. The gladiolus is enlarged, but generally to a much less relative extent than the *manubrium*, which appears entirely out of proportion to the former. The *xiphoid process* shares in this general increase in size and is rough and often covered with tuberosities.

The arch of the *ribs* is free and has more of the circular type than in the normal. The ribs themselves are broad and thick, the thickening being most marked on the lower borders, where the intercostal arteries pass. The points of muscular attachment on the ribs are enlarged and rough; the head and neck ordinarily show great hypertrophy.

Upper Extremity.—The changes in the *clavicle* are among the most marked of the osseous variations seen in acromegalia, but the same anomalies are often present in the claviculæ of healthy persons of unusual muscular development. The curves are accentuated, while the shaft of the bone is massive and heavy and yet not sufficiently to be in proportion to the enormously enlarged ends. Both the sternal and acromial ends show this enlargement, but, as a rule, it is most pronounced at the acromial extremity where the surface is very rough and often covered by exostoses. Notwithstanding the exaggerated curvature of the bone, the absolute length of its span is increased, so giving the broad and overhanging appearance to the shoulder cap.

Changes in the *scapula* are mostly limited to the spine, and the acromial and coracoid processes. The last mentioned protuberances are enlarged, rough and like other points of muscular origin, frequently covered by exostoses and spines of new-formed bone. The remaining portions of the scapula usually show very few changes,

except at the points of muscular or tendinous attachment, where more or less hypertrophy and roughening are found.

The *humerus* is generally not much changed, but some increase in length is at times present; the increase here, as seems to be the case in all the long bones, is limited principally to the epiphysial extremities. Frequently the head of the bone is considerably enlarged and the tuberosities are also increased in size and rough, as are all the muscular attachments on the upper third of the bone. The shaft does not usually show much change, aside from a general exaggeration of the lines of insertion of the muscles of the shoulder and forearm. Hypertrophy of the distal extremity of the humerus is not unusual and when present is most plainly seen in the external and internal condyles, where spines and exostoses are not infrequent.

The *radius* and *ulna* as a rule, show very slight changes in the shafts though, as has been so frequently stated of the other bones, all lines of muscular attachment are enlarged. The heads of the bones are sometimes enlarged, more particularly the olecranon process of the ulna; sometimes this is not the case, but when the corresponding articular surfaces are enlarged, then the heads of both bones of the forearm are also hypertrophied. When there is no increase in the size of the distal extremity of the humerus, the heads of the radius and ulna are of usual size. The distal ends of the bones of the forearm are quite constantly changed, and of the two bones by far the most marked variations are to be found in the radius. Quite frequently, even in well-marked cases, the tip of the ulna is apparently normal, while the associated portion of the radius is considerably enlarged and its articulating surfaces deepened.

The bones of the *carpus* are usually somewhat increased in size and their surfaces are rough, especially on the palmar aspect. The grooves traversed by the tendons and vessels are frequently deepened, but as a rule, these bones show very little which could be described as characteristic. The *metacarpal bones* are still less altered, but the tubercles for the insertion of the interossei muscles are frequently exaggerated and, in some cases, the bones are enlarged. The *phalanges* show in themselves very little that is characteristic but appear somewhat large in proportion to the corresponding metacarpal bones, and the epiphysial ends are often rough with osteophytes. The ungual phalanges, however, show quite striking peculiarities (Plate II, Fig. 1); their distal periphery is frequently studded with osteophytes and the entire ridge of bone supporting the pulp of the finger, is markedly hypertrophied. The bases of the bones may also show hypertrophic changes of a considerable degree. The greatest variations from the normal in all the bones of the hand, it should be noted, are those of the palmar surfaces of the bones. Much has been written concerning the condition of the phalanges in the disease, and some have described these changes as typical of acromegalia, but that they are far from typical of any one disease is clearly shown by the fact that similar changes are noted in hands which belong, in so far as we can tell, to perfectly normal individuals. Especially is this the case, as can be noted in any anatomical laboratory, in the hands of those accustomed to heavy manual labor, or in those persons who have highly muscular hands. The writer has noted, for intance, the thickened phalanges in professional pianists. Sternberg has directed especial attention to this fact in his recent monograph. In the "type géante" hand of Marie,

it must be remembered that none of these changes are found, but that the bones of the hand are simply symmetrically enlarged. It seems that the typical picture presented by the acromegalic hand is brought about more by the hypertrophied soft parts than by bony changes.

Pelvis.—The bones making up the pelvis do not show very characteristic variations from the normal. In general, they are large and heavy and are such as would be expected in one of ponderous development. The crests and spines of the *iliac bones* and the tuberosities of the *ischiæ* are enlarged, rough and prominent. All the other seats of muscular attachment show about the same condition.

Lower Extremity.—Alterations very like those of the upper extremities are also present in the skeleton of the thigh, leg, ankle and foot. On the *femur* we find the trochanters enlarged, the spiral ridge augmented; indeed every area of muscular or tendinous attachment is rough and hypertrophic. Over the posterior surface of the shaft, the ridge intervening between the attachments of the vastus internus and the vastus externus is raised, sharp, and rough with osteophytes. It may be said that all the borders and lines of the bone are exaggerated and "over-outlined." The lower epiphysis of the bone shows the same general changes, often to a more marked degree than the head. The femur, as a whole, may be said to be hypertrophied.

The *patella* is almost invariably considerably enlarged in all its diameters; both anterior and posterior surfaces are rough, and the periphery of the bone is frequently covered by tubercles and grooved depressions. The articulating surfaces of the *tibia* are deepened; the lines of insertion of the ligaments of the knee joint are rough.

As a rule, the head of the *fibula* shows few variations, but its shaft, like that of the tibia, is massive and stout. At the lower extremities of the bones, we find the grooves for the passage of tendons and vessels hollowed out, deepened and their edges often surrounded by exostoses. In occasional cases, the lower articulating surfaces of the bones are deepened.

The bones of the *tarsus*, as a rule, show less evident changes than those already described in the carpus. An exception must be made, however, in the case of the *os calcis*, which is usually not only considerably enlarged as a whole, but especially in those portions which give insertion to tendons or muscles. The changes of the *metatarsus* and *phalanges* are, in general, quite similar to those of the corresponding bones of the hand, though usually rather less marked. Beyond these changes the alterations in the pedal bones do not appear to merit special mention.

Reports of the *microscopic examination* of the bones in acromegalia vary so greatly in their import that very little can, of a certainty, be said of them. A systematic microscopic examination of all the bones, in any single case of acromegalia, is not yet published, most investigators being content with examination of those bones, or portions of bones which show the most striking macroscopic lesions. The periosteum is universally thickened, as are also the tendons and aponeuroses, wherever attached to the bones. In the average case, the cartilages, especially those covering the articular surfaces, are more or less enlarged, and microscopic examination gives evidences of proliferation of the cartilage cells.

The compact bone appears in certain cases to have been replaced by bony tissue of a more cancellous nature. In others, as in the first two cases reported in this paper,

there is apparently increase of the compact tissue, with a relative diminution of the cancellous portions of the bone. In the medulla of the bone, changes tending toward construction are also very evident.

In a general consideration of the changes of the osseous system in acromegalia, the fact must not be lost sight of that often these variations are of far less extent than those of the soft parts, and in some cases, the osseous lesions appear to have been very slight indeed. As one of the most prominent and constant features of the disease is the hyperostosis, the exact significance of this lesion is a question of considerable importance. Similar bony changes, especially those of the extremities and of the long bones, are found in individuals not afflicted with acromegalia, and such instances are even commonly seen in subjects whose muscular development is above the ordinary. It is noticeable that the seats of greatest growth in the bones are, in general, those areas where there is growth normally or where, through active function of the parts, augmentation of the bony structure naturally takes place. This is instanced in the enlarged tuberosities and seats of muscular and tendinous attachment found in the skeletons of athletes. Finally it appears that this particular variety of the bone changes—the hyperostosis and accentuation of the musculo-tendinous attachments—are simply localized expressions of the general connective tissue hyperplasia, due to the relatively greater amount of function exercised at these points.

The changes found in the pituitary fossa and in the surrounding bones are, of course, entirely secondary and simply those which would be induced by a tumor of any nature whatever growing in the same place.

Muscles.—Lesions of the *involuntary muscles* are not reported in any of the papers which the writer has reviewed up to the present date. In our own cases few lesions of involuntary muscle were found and we feel warranted in saying this much: hypertrophy of the involuntary muscle bundles does not take place; that on the contrary, in at least certain areas of distribution, as in the walls of the medium-sized blood vessels, the involuntary muscle cells are, at times, found more or less atrophied and degenerated. Probably this is merely secondary to the primary lesions in the vascular system; due possibly to the pressure on the muscle fibres by the increased interstitial tissue in the walls of the vessels.

Abnormalities of the *voluntary muscular system* are almost universally reported (Plate IV, Fig. 6). In the great majority of cases the muscular power is said to be diminished, and in the larger proportion of the cases in which the condition of the voluntary muscles has been definitely noted, these muscles are said to have been atrophied, but Mosler has reported a case in which they were hypertrophied. It is important to notice that the muscle may be of quite normal size for an individual of ordinary stature and yet be small in proportion to the greatly enlarged bony framework; thus, it does not seem out of place to record under the head of hypertrophied musculature some of those cases in which the muscles were reported as natural and in which more or less gigantism was present. As we have already seen in nearly all cases, the tongue, which is largely a collection of voluntary muscles, is reported as hypertrophied. Thus macroscopically, we find that in acromegalia, and in well-marked cases of the disease, the voluntary muscles may be atrophied, hypertrophied or normal. Unfortunately,

in the majority of cases, no microscopic examinations have been made, but, where this has been done, the reports are quite constant and unanimous. Arnold reports various types of atrophy and quotes as confirmatory the work of Fraenkel, Babriski, Schultze, Eisenlohr, Hoffman, Langerhans, Kopp, Fürshner and Dinkler. Sternberg, in his recent monograph, says that microscopically all forms of degeneration and atrophy of the muscle fibres are found. Others, as Goldin and Kershner, have reported the muscle fibres normal. An increase in the connective tissue of the framework of the muscle is generally admitted and to this, not to hyperplasia of the muscle cells, is probably due the fact that the size of certain muscles is found augmented, as is the case in the tongue. The degenerations so constantly found in the voluntary muscle fibres are one of the most interesting features of the disease and the explanation of this abnormity is by no means clear. It is thought by some to be secondary to changes in the nerve centres or in the nerve trunks, and by others to be a primary degeneration of the muscle cells, due to deficient or altered nutrition, or perhaps, a result of the connective tissue hyperplasia. This being the general anatomical condition of the voluntary muscles, it is most curious to note that the electrical reactions are nearly always normal, even in those cases which show considerable muscular atrophy. The significance of the muscular atrophy seems all the more obscure when we consider it in comparison with the hypertrophied bones, the changes in which would seem to indicate an increased, rather than a subnormal muscular development and function.

Blood Vessels.—Changes in the blood vessels are constantly present in acromegalia; these are of so great importance that Klebs was inclined to look on them

as primary and as the most characteristic pathological evidence of the disease. A study of the literature of acromegalia, together with an especially careful observation of the conditions presented by the vessels in Case II, has convinced the author also that these alterations are among the very first manifestations of the disease and that they are most suggestive as to the true character of the malady. The writer, however, would by no means be understood as endorsing the theory of Klebs in regard to the relation of the thymus gland to acromegalia, nor do we believe the vascular changes to be primary in, or dependent on, alterations of this body.

Lesions of the vascular system are present in every part of the body; they are found in the large vessels, the aorta and pulmonary arteries, in the trunks of the medium and small sized vessels, and finally, they are everywhere present in the capillaries. It is, however, in the terminal vessels that we find the changes most marked, especially in the trunks of the subcutaneous tissues of the extremities. In short, the vascular lesions are found in their most exquisite type, in those portions of the body where the circulation is slowest and where capillaries are most numerous. The adventitia of the vessels is increased, especially in the smaller arteries. In the viscera, proliferation of the adventitia often extends to the general perivascular connective tissue. In the media, the muscle fibres are diminished and encroached upon by the increased interstitial tissue growing between the muscle cells. In the smaller and middle sized arteries, the subendothelial layer of connective tissue is almost always thickened. In the intima of the smaller arteries we find the endothelial cells showing every evidence of proliferation. This same process extends into the capil-

laries where mitotic figures are quite commonly found in the nuclei of the endothelium (Plate IV, Fig. 3). A widening of the capillary channels is frequently evident and, not uncommonly, areas showing the actual formation of new capillaries are seen. The capillary changes are all found in most marked degree where connective tissue hyperplasia is most active. This is especially true in the subcutaneous connective tissue and in the interstitium of the various viscera.

Heart.—The heart is usually more or less enlarged, generally with the hypertrophy most marked in the walls of the left ventricle; the heart may however, be normal, or even atrophied (Henrot). Endocarditis, valvular or coronary disease, may or may not be present, and seem to bear no constant relation to the malady. Microscopically the heart-muscle frequently shows changes similar to those already described in the voluntary muscle fibre, and such an instance is well exemplified in the heart of Case II. (Plate IV, Fig. 7). However, as in Case I, the variations in the heart-wall may be entirely limited to the interstitial and vascular lesions common to nearly every part of the body.

Blood.—Morphological studies of the blood have been made in but a few cases of acromegalia and, from these, it does not seem likely that the microscope will demonstrate any constant change or series of changes in the blood which will be at all characteristic of the disease. Yet the active proliferation of the endothelial cells of the vessel walls, together with the pronounced nutritive alterations in acromegalia, leads us to the conclusion that changes in the blood are present, and are quite likely inductive of many of the disease manifestations. Such abnormalities, if they exist, are, in all probability, *chemical*

in nature, and it seems that a thorough chemical study of the blood in acromegalia would very likely throw much light on the disease. Unfortunately no work of this nature has as yet been recorded.

Respiratory Organs.—The respiratory tract shows, as a rule, comparatively few changes. The changes in the nose are chiefly of the external aspect, already described, but hypertrophic rhinitis is a common condition in these cases. In certain cases the thyroid cartilage is generally enlarged; in these instances the lumen of the trachea is more or less increased and its mucous membrane, with the epithelium covering the vocal cords, is thickened; this condition explains some of the alterations in the voice which frequently accompany acromegalia.

In the lungs the changes are chiefly secondary, but, not infrequently, they represent terminal processes which may finally result in death; thus, we usually find more or less chronic bronchitis, emphysema, passive congestion and oftentimes, depending on other diseased viscera, the so-called cardiac and hepatic pneumonias.

Digestive Tract.—The enlarged tongue, with its prominent papillæ and thickened epidermis, together with the deep and broad buccal cavity, have already been mentioned. The mucous membrane lining the oral cavity is, like the skin, thickened and hypertrophic. The lymph nodules, situated on the posterior surface of the tongue, as well as those of the pharynx and the tonsils, are usually enlarged. The œsophagus presents no abnormalities. The stomach is more or less enlarged in the majority of cases. Its mucous membrane as a rule, considering the age and habits of the patient, is in a normal condition; but gastric carcinoma has been reported by Dallemagne, and Boltz cites a case in which ulcer of the stomach was

present. It is evident, however, that such coincidents are entirely foreign to the pathology of acromegalia in itself. In those cases in which excessive appetite is a symptom, we are liable to find the stomach considerably dilated, and this condition may extend on into the small and large intestine, both of which are then proportionately large. Even in these cases abnormalities of the mucous membrane are wanting. Frequently, all the lymph follicles of the gastro-intestinal tract are enlarged. The salivary glands are not reported as altered in any of the cases reviewed by the writer, but it seems probable that the general interstitial change might, in some cases, affect these structures also.

In the pancreas, however, changes are quite constant, especially in those cases which exhibit glycosuria. These lesions are usually interstitial in character and, in brief, are those which have been reported in pancreatic diabetes. (Plate IV, Fig. 2). Dallemagne reports one case in which the changes were present without glycosuria and, in Case II, in which glycosuria was present, it is interesting to note that interstitial pancreatic changes were slight. Parenchymatous pancreatis has also been found, and Pineles describes a case in which fat necrosis was present. It seems quite probable that the glycosuria, so frequently present in acromegalia is due, in great part, to these pancreatic changes. In Case I the diabetes is undoubtedly of the "bronze" variety.

In the liver hypertrophic cirrhosis is usually found and is frequently associated with more or less fatty degeneration of the liver cells. (Plate IV, Fig. 1). Often chronic congestion is evident.

Lymphatic System.—It has already been mentioned that the lymph glands are generally more or less enlarged in

acromegalia. This enlargement is usually of an interstitial character (Marie and Marinesco) and is frequently accompanied by a pigmentary deposit in both the stroma and the lymph cells. The lymph nodes of the mesentery and of the intestinal tract generally, are particularly liable to these changes, but, as already intimated, they are quite common wherever lymph adenoid tissue is present.

The spleen also, in acromegalia is usually enlarged, though it is reported in some cases as normal (Mossé), or even as small (Pineles). Microscopically it shows the same general interstitial increase present throughout the previously mentioned portions of the lymphatic system. The vessels in the spleen often show changes to a remarkable degree. As in Case I, considerable pigmentation of the viscus is sometimes present.

The thymus gland (Plate IV, Fig. 5), which should perhaps be classed among the lymphatic organs, persists in a considerable per cent of the cases. Klebs was the first to call particular attention to this abnormality and, as will be stated at more length later, was inclined to consider it as an etiological factor of the disease. In those cases, in which the gland is found persisting, it presents no peculiarities of structure, or as in Case II, it may show indications of a normal disintegration and replacement.

The tonsils have already been mentioned as enlarged.

Urinary System.—The kidneys (Plate III) in acromegalia, as a rule, are enlarged. They may, however, be extremely small, representing the final stages of a chronic interstitial nephritis. The cells of the tubules may show degenerations of every variety and degree, from slight to extreme. Interstitial increase, of more or less extent, is apparently invariably present. The connective tissue may be in the stage of hypertrophic

growth, or, on the other hand, contraction and sclerosis of the organ may be established, or fully advanced. The kidney changes are, of course, by no means characteristic of acromegalia; they are simply those of a chronic interstitial nephritis. The bladder frequently shows evidences of considerable distension, especially in those cases where polyuria is present.

Genital System.—As already mentioned under the general description of the disease, we often find hypertrophy of the external genitals; this enlargement, microscopic examination has shown to be due to increase of the large amount of connective tissue normally present in these organs, together with a capillary growth and venous congestion. Dercum has reported a case of hypertrophy of the testes, but usually these glands, together with the prostate and urethra, present no significant abnormalities. On account of the usual establishment of the menopause coincident with the development of acromegalia, the internal genital organs of the female, have been very thoroughly studied, but, in so far as etiological factors are concerned, with disappointing results. The ovaries and uterus show nothing distinctive from their usual conditions when the menopause has become established, hence they are usually reported as atrophied, or of the infantile type. In female acromegalics, the form of the body often loses its feminine type, but this is by no means characteristic of the disease, and these same alterations may take place when, for any reason, an early menopause is established, such as is often the case following ovariotomy in young women. In so far as explaining the onset of an early change of life in the development of acromegalia, or as to establishing any connection between the general manifestations of the disease and those of the generative organs, pathological studies have yielded no result.

Chapter VIII.

PATHOLOGICAL ANATOMY.—*Continued.*

Nervous System.—It is quite natural to expect pronounced abnormalities in the various portions of the nervous system, in a disease which exhibits so many neurological symptoms, and the examinations of the nerve tissues have shown quite extensive and general changes.

Peripheral Nerves.—The trunks of the peripheral nerves are, for the most part, enlarged; this is directly due to an increase in the connective tissue of the endoneurium and perineurium. Often the sheaths of the nerve trunks also show considerable thickening. This general connective tissue hyperplasia, frequently, so encroaches on the nerve fibres as to destroy them, and degenerated nerve fibres are quite commonly found, some of which may show complete axis cylinder destruction (Arnold, Comini). These conditions may persist throughout the entire nerve trunk, extending even into the nerve roots. (Arnold, Duchesneau).

Ganglia.—In the posterior root ganglia also, we find the connective tissue elements greatly increased, so that even macroscopically the ganglia are often considerably enlarged. Microscopically, the ganglionic cells are sometimes pressed upon and atrophied (Marie, Marinesco). Arnold reports that he found vacuoles in the nerve cells. With the modern methods of neuro-cytology, we would expect to acquire a more definite knowledge of the changes in the nerve cells, but in Cases I and II of the author, the alterations in the ganglion cells were slight.

It is difficult to determine whether the nerve cell lesions are secondary, perhaps directly dependent on the connective tissue hyperplasia about the cells and fibres, or are

primarily due to defective nutrition of the ganglion cell bodies. Perhaps these ganglionic changes are wholly, or in greater part, responsible for the degenerations and atrophies which take place in the muscles of the voluntary system.

Sympathetic Ganglia.—The changes in the sympathetic ganglia and trunks have been made the subject of special study by several very prominent investigators, among whom are Marie, Marinesco and Arnold, and have been looked upon by many as factors of an etiological nature. Finding, as we do, such pronounced change in the blood vessels, it does not seem at all strange that lesions in the sympathetic ganglia should be present; but a view, intimating a dependence or relation of the vascular changes to the lesions in the sympathetic system is not in accordance with our own ideas expressed at the close of this paragraph. In general, the changes in the sympathetic ganglia are very similar to those already described in the ganglia and trunks of the cerebro-spinal system. In some cases, the size of the ganglia is considerably increased, (Arnold, Marie, Marinesco), and microscopically, the connective tissue web is thickened and proliferating. The ganglion cells are often reported as exhibiting evidences of degeneration. The changes in the semilunar ganglion cells represented in Plate VI, Fig. 4, are difficult to interpret, because of the possibility of having been induced by the toxic action of the terminal infection (peritonitis). To this is added the complication of a rather late autopsy—12 hours after death—which brings up the possibility of the production of post-mortem artefacts in the cells. The fact that post-mortem cytologic changes are not present elsewhere in the nervous system does not lessen the possibility of their occurrence in the

semilunar ganglion, because of its proximity to the gut and consequent exposure to intestinal putrefaction. Arnold has found vacuolization; not infrequently, considerable deposits of pigment are seen within the cytoplasm. But, as in Case II, the ganglion cells may be normal, the Nissl bodies are present in normal arrangement, volume and shape and show no deviations in their staining reactions; and the pigmentary deposit is not abnormally abundant. The sympathetic ganglia in the case reported by Gauthier were also normal. It is advisable, at this point, to call attention to the fact, that the interstitial hyperplasia is by no means a lesion characteristic of the sympathetic system, but is simply an extension of the general process so often alluded to. The growth of connective tissue in the sympathetic may depend in part on lesions in the walls of the vessels; or both may be referable to the common factor of deranged nutrition.

Cord and Medulla.—The pathological findings in both the cord and medulla differ greatly. Virchow, and also Fritsche and Klebs, have reported hypertrophy of the medulla. The spinal cord was enlarged in the case reported by Linsmayer. Many observers have reported various degenerations in the cord. Baruch's case was associated with symptoms of syringomyelia; Debierre gives a case with diseased posterior columns, while Arnold, Dallemagne and Tamburini have found at autopsy, irregular degenerated areas in the cord, affecting, however, no special place with any degree of constancy. Usually, as in the first two cases reported in this paper, no abnormalities of either the medulla or cord are found.

Brain.—No constant changes are found in the brain, but, as is the case with every other organ of the body in acromegalia, the encephalon may be enlarged (Fritsche,

Klebs, Holsti), though the increase is rarely proportionately as great as that of the body. Usually, as in the cases of the author, few microscopic changes of note are found. Demonstrable cytologic degenerations are absent, though interstitial and vascular lesions are sometimes reported.

We sometimes find a general enlargement of all the internal viscera in acromegalia; a condition termed "*splanchnomegalia.*" As one would naturally expect, it is most common in acromegalics of the gigantic type, though sometimes found in cases in which general enlargement of the body is not present.

Eye.—Of all the special sense organs, the eye is most affected in acromegalia. Strzemińiski and Uhthóff have written extensive studies on the ocular conditions, giving a very exhaustive description of the symptoms and lesions and their causal relations. In brief, the changes may be said to be simply those which would result from the presence of any tumor growing in the region of the pituitary body, pressing on the optic chiasm and the optic nerve roots, as well as on the vessels supplying the orbit. Hence we may have, depending in each case on the amount and area of pressure, various degrees of optic neuritis, narrowing of the optic fields, exophthalmus and, finally, in extreme cases, amblyopia. In some cases the trunks of the fourth and sixth nerves become involved, and corresponding muscular insufficiencies develop. (Plate I, Fig. 1). Hypertrophy of the lachrymal gland was found in a case reported by Orsi.

Ear.—In the ear, we find at times more or less occlusion of the meatus, brought about by the formation of

osteophytes which project into the bony canal. Otherwise the ear is not specially affected in the disease.

Taste.—As already mentioned, the enlarged tongue is one of the marked evidences of the disease. The papillæ, especially those of the fungiform variety, are often considerably hypertrophied. This condition, together with the overgrowth of the adenoid nodules of the posterior portion of the tongue, is probably responsible for the deficient sense of taste sometimes present in acromegalia.

Smell.—The mucous membrane of the nasal tract is usually hypertrophied, sometimes to such an extent as to seriously occlude the nasal passages. As is usual in hypertrophic rhinitis, diminished sense of smell results from this change.

Ductless Glands.—The abnormalities found in these bodies, have been reserved for consideration last, since it is in these, and especially in one of them, that we find those changes which are now generally believed to be of greatest importance in the pathogenesis of acromegalia. Under the heading of the ductless glands, it seems right to group three structures, viz., the adrenal bodies, the thyroid gland and the prehypophysis, or anterior lobe of the pituitary body.

Adrenal Bodies.—In those cases where general enlargement of the internal viscera is present, the adrenals are also usually found increased in size but, as a rule, these structures present nothing of significance, either in their gross or microscopic appearance.

Thyroid Gland (Plate IV, Fig. 4).—The variations in the size and structure of this important gland have received a great amount of attention in the study of acromegalia; partly, for the reason that changes in this body are fairly constantly found in this disease, and also, because acro-

megalia bears a strong resemblance, in many respects, to myxœdema in which the important rôle of the thyroid has been well established.

In regard to size, the thyroid gland is often reported enlarged (Duchesneau, Ruttle, Strümpel, Murray, Gebhardt, Fratrich, Hare, Pel). In other cases, it is stated as normal, and quite often no mention whatever is made of its condition. Murray reports two cases with pronounced goitre, and Osborne has recently found a case with a supernumerary thyroid. The descriptions of structure also differ quite widely. The interstitial framework of the gland is usually increased. In the cases with hypertrophy, the enlargement seems generally due to an increase in the number and size of the colloid containing alveoli. Burg, Pineles and Kanthack have found cysts (probably colloid) in the substance of the thyroid. Hyaline degeneration of the vessel walls has been reported by Arnold and, in his case, the degeneration was so extensive as to involve not only the vessel walls but also the surrounding tissues. Duchesneau has found carcinoma of the thyroid in one case. As a whole, we must conclude that no constant set of changes is found in the thyroid gland in acromegalia, but that the body is almost always diseased in one way or another. Atrophy is, perhaps, the most common lesion, but hypertrophy is not infrequent, and in a certain per cent of cases, no abnormality of this gland is present.

Hypophysis Cerebri.—In the series of autopsies which the author has been able to collect, nearly all have shown upon gross examination noticeable enlargement of this body, while atrophy has never been reported except in the single instance of Mossé and Daunic, and only very exceptionally has it been stated as normal in size. In most

of the cases, the enlargement had taken on the form of a tumor growth. If it were permissible to include in this list the instances where the clinical symptoms point distinctly toward a tumor growing in the region of the pituitary body, but in which no autopsy was performed, our series of cases would be greatly enlarged. Indeed, the symptoms of pressure, neuralgia, migraine and optic disturbances, all indicative of intracerebral growth, are so constant in acromegalia as to be mentioned among the most common symptoms of the disease (Marie, Souza-Leite, Arnold, Collins, Dercum, Sternberg). Tamburini finds the pituitary enlargement undoubtedly present in seventy per cent of the cases collected by him, and further, he excludes several cases in which this lesion was not present, as not being acromegalics, so bringing his percentage up considerably higher. Putnam finds the diseased hypophysis certainly present in ninety-two per cent of his series.

Notwithstanding the almost constant occurrence of enlargement, or tumor of the hypophysis in acromegalia, cases are reported in which this gross lesion was not present at autopsy, and on account of the rarity of such instances they are deserving of the most careful consideration. *It will be noticed at once that such cases are almost exclusively among those first reported and they were, for the greater part, published at a time when the disease was unfamiliar and when the differential diagnosis from the many allied conditions was very poorly defined.* The writer agrees with Tamburini, that a considerable number of these cases were not acromegalics. Now that acromegalia has become quite well recognized by general practitioners, we find very few instances recorded in which the indications of this enlargement are not present.

In every autopsy reported (excepting in a single case

of Dallemagne) these changes, *i. e.*, enlargement or tumor growths of the pituitary body, have been confined to, or have apparently originated in, the anterior lobe of the hypophysis. In a considerable number of cases, however, where the pituitary body is simply stated as "enlarged" and no microscopic examination recorded, it is of course impossible to exclude involvement of the posterior lobe. It is only possible here to utilize those reports in which microscopic, or at least thorough macroscopic observations have been made, and a review of such records warrants the statement made above. Changes of minor importance, however, have been reported in the posterior lobe, such as the universal interstitial overgrowth, and hyaline degeneration of the vessels (Arnold). Dallemagne, however, found both cystic degeneration and hypertrophy of the posterior lobe in one of his cases. Not infrequently, as in Case II, the growth of the prehypophysis has been found to invade the tissue of the posterior lobe.

Although it is now universally acknowledged that we find either hypertrophy or tumor of the prehypophysis in acromegalia, yet the reports as to the precise nature of this overgrowth are at the widest variance.

Where microscopic examinations have not been recorded the pituitary is often simply mentioned as enlarged (Dana, Rathmell, Dalton, Osborne). In other cases the enlargement is found to be of a hyperplastic nature (Plate VI, Fig. 1). (Gauthier, Cepeda, Holsti, Fritsche-Klebs, Dallemagne, Bonardi, Furnivall, Schultz and Jores, Brooks). Very closely allied to the hyperplasias are those instances in which prehypophyseal adenomata were found (Plate VI, Fig. 2). (Marie, Marinesco, Linsmayer, Tamburini, Boltz, Klebs, Bailey, Brooks). Sarcoma of the pituitary is one of the most common of the conditions reported. (Mossé and

Daunic, Wolf, Caton and Paul, Strümpel, Dallemagne, Griffith, Pineles, Hansemann). Lymphomatous enlargement is recorded quite frequently, and the author was at first inclined to place one of his cases in this class of which examples have been reported by Brigidi, Claus and Van der Stricht, Comini, Sigurini and Caporiacco and Henrot; probably the case of Arnold, which is stated as resembling lympho-sarcoma, should also be included in this list. Two cases presenting glioma of the hypophysis are on record. (Roxburgh and Collis, Bury).

In several of the cases, in which the prehypophyseal hyperplasia was present various degenerations were found, most commonly the colloid variety. This appears to have been the condition present in the hypophyses of the cases reported by Dana, Dalton and Holsti and Dallemagne, and this same process, but in a more extreme degree, was found by Fratritch, and by Boyce and Beadles in one of their autopsies. Probably these large areas of colloid degeneration simply represent hypertrophy of the colloid-containing acini which are normally found in the hypophysis cerebri. In many cases where the growth is hyperplastic or adenomatous, a granular degeneration and breaking down of the cells is noted. This is especially common in the central parts of the growth. A similar condition is often found in normal prehypophyses. It is practically impossible to distinguish, in a certain class of cases, between hyperplasia and adenomatous growth, as is well instanced in Case I, in which the anterior lobe of the hypophysis was in itself the seat of hyperplasia and also contained a neoplastic growth of adenomatous nature; indeed, in so far as practical purposes are concerned, the cases of adenoma may be included with those of hyperplasia, since the two conditions are so closely allied.

The cases reported as sarcoma are of great interest, because it is very questionable if they are really examples of sarcoma.

In several instances lympho-sarcoma is reported, but the descriptions of these growths lead one to believe that, in many of the cases, they should be classed among the adenomas or hyperplasias. With the exception of a single instance (Mossé and Daunic) all the tumors grouped under the head of sarcoma are of the round-cell variety where the special kind is mentioned at all, and as such they would be differentiated with some difficulty from a growth of epithelial origin, springing from, and following, the type of the highly vascular prehypophysis. It is significant also that in all the cases reported as sarcoma no instance is recorded in which the growth was secondary or where metastases were produced.

In reviewing the literature of acromegalia, one meets with a great obstacle in the fact that even in many of the cases in which otherwise careful microscopic examinations are recorded, the cytological structure of the hypophysis, or hypophyseal tumor, has been neglected. This is most unfortunate, since it is quite possible that in all cases the *cellular characteristics* of the growth are the same.

Chapter IX.

General Considerations of the Pathogenesis of Acromegalia.

Many theories have been elaborated concerning the pathogenesis of acromegalia. These theories, in their entirety, have covered nearly every possible field, but, as the pathological anatomy of the disease has become better known, and as the differential points between acrome-

galia and similar conditions have become more clearly defined, the speculations as to the productive agent or agents have become less numerous. In this paper it seems necessary to consider only the principal theories of the pathogenesis based on patho-anatomical studies of the disease; of these the following are the most important:

I.—Alterations in the structure and functions of the sympathetic nerves and ganglia.

II.—A disease primary in the connective tissues bringing about active increase of the connective tissue elements throughout the body.

III.—Changes following functional disorders of the genital organs.

IV.—A budding of the vascular canals originating in and dependent on persistence of the thymus body.

V.—Changes in the secretion of the thyroid, accompanying hypertrophy or atrophy of the gland.

VI.—Disease of the pituitary body.

VII.—A specific lesion of the prehypophysis. Increase of the cells and secretion of the gland. Hyperplasia or adenoma.

I.—CHANGES IN THE SYMPATHETIC NERVOUS SYSTEM.

The changes found in the trunks and ganglia of the sympathetic nervous system have been thought by many to be of primary etiological significance. These changes, as has already been noted in the chapters on pathological anatomy, are two—interstitial increase in the ganglia and about the fibres in the nerve trunks; and—occasional degeneration of the sympathetic ganglion cells.

The interstitial increase we certainly cannot consider as characteristic, since, as we have seen, it is present throughout the entire body and in some places, as about the vessels,

to a much greater degree than in the sympathetic trunks and ganglia; hence, it seems rather too arbitrary to attribute the general disease process to the local extension of the general connective tissue hyperplasia in some special organ. Interstitial increase in the sympathetic is by no means found in acromegalia alone but is frequently reported in widely different disorders.

Degeneration of the sympathetic neuron cell bodies, especially the chronic phase, is as yet quite obscure, and, when ascertained by methods used before the application of recent cytological technique as typified by the Nissl procedure, are really of comparatively little value. Unless relating to gross and destructive changes, it is best to discard the results of these examinations and to rely only on the examinations conducted on fresh autopsy material, with the careful and exact modern technique of the Nissl type, which demonstrates cytologic structural details. From this standpoint reliable data of sympathetic cellular lesions are altogether too limited to afford a basis for any positive general statements as to their *regular occurrence* and significance in acromegalia. In our own cases chronic degenerative lesions in the sympathetic ganglion cells as demonstrated by the Nissl method, are apparently absent.

Anyone who looks forward to the great amount of cytological research of the sympathetic awaiting investigation in the future, and who appreciates the probable importance which acute and chronic degenerative changes in the parenchyma of this system will assume in the next few years in general somatic, nervous, and possibly even in mental disease, naturally hesitates in excluding too hastily the causal role of lesions of the sympathetic, in disorders of the vegetative or nutritive functions, such as acromegalia and allied affections. But the difficulty with

the theory of the sympathetic origin of acromegalia is that the occurrence of cellular lesions in this system is the exception rather than the rule.

Where degeneration of the sympathetic ganglion cells is found associated with acromegalia, we should, in discussing its significance, be careful to eliminate other exciting causes than those peculiar to acromegalia. For instance, the action of secondary auto-intoxication, such as diabetes or terminal infection, can not at present be positively excluded as a factor inducing degeneration of the sympathetic ganglion cells.

Future researches may show that the sympathetic ganglion cells are no more regularly affected in acromegalia than in a great variety of other chronic diseases accompanied by pronounced vascular lesions or persistent disturbances in nutrition. While the presence of pigment granules is of profound significance, little is to be gained by a discussion of "pigmentation" and "pigmentary degeneration" of the sympathetic in acromegalia because these terms, as generally used, are almost meaningless.

The connective tissue overgrowth in the sympathetic, judging from our cases, is not consecutive to death of the parenchyma, as is frequently the case in actively functionating organs. It is a process of growth taking place in the stroma independently,—an extension of the general connective tissue hyperplasia. The ganglion cell degenerations, and it is very doubtful if they occur at all constantly, are probably only secondary complications accompanying rather advanced vascular lesions or defective nutrition in terminal stages of the disease. If, however, certain of the sympathetic cells should perish by reason of the more severe alterations of nutrition in the later stages of the disease, or through other complicating

factors, we might have, in addition to the primary growth of connective tissue, replacement hyperplasia filling the gap left by the dead parenchyma cell. The subject of degeneration of the sympathetic ganglion cells in general requires further investigation before it can be discussed clearly in relation to acromegalia. *Thus far it has not been demonstrated that this lesion is at all regularly associated with the disease, and there seems to be no sound basis for regarding lesions of the sympathetic as even a proximate causal factor in the induction of the disease process. Lesions of the sympathetic, then, appear to be wholly secondary manifestations* to the general disease process.

II.—PRIMARY DISEASE OF THE CONNECTIVE TISSUE INDUCING GENERAL INCREASE OF THE CONNECTIVE TISSUES THROUGHOUT THE BODY.

Increase in the volume of certain of the mesoblastic structures, such as the subcutaneous connective tissue, the visceral interstitium, connective tissue of the vessels and peripheral nerves and portions of the bones, etc., is the one uniform and definite accompaniment of the disease process in acromegalia. That it is present to a marked degree, even in the early stages of the disease, seems established by the findings in Case II, in which the disease had apparently progressed to only a slight extent. The connective tissue proliferation seems to follow the track of the blood vessels and reaches its maximum in certain special parts of the body, as beneath the integument of the hands and feet.

But this change cannot arise spontaneously within the connective tissue itself. There must be some ulterior factor which first excites the abnormal growth and which by its persistent action on the connective tissues constantly

augments their growth. In other instances of pathological overgrowths of connective tissue, we can frequently associate them quite definitely with extrinsic exciting causes, such as arteritis or toxæmia. Indeed without taking into account the exciting cause and expressing even in general terms the *modus operandi* of the hyperplasia with reference to this cause, the connective tissue theory is not a theory at all. It is merely the statement of a fact, an effect of the disease process and *not in the least an explanation of the process itself.* Hence in this guise this so-called theory deserves no further discussion, and ought to be thrown out of the explanations of the disease process in acromegalia altogether. We can return to the question of connective tissue hyperplasia in the discussion of the hypophyseal lesion.

III.—THE GENITAL THEORY.

It has been thought by some writers that the abnormalities in acromegalia were primarily due to genital disturbances. This supposed causal relation of the lesions of the genital organs to the process in acromegalia is a mere surmise and hardly worthy of discussion. It is not a theory, for it explains nothing,—it merely states the fact that the genital organs undergo pathological changes in the malady.

The changes in the genital organs are among the effects of the general disease process. Probably the menstrual disorders and the early establishment of the menopause result from the alterations of the blood and possibly also from the increased development of connective tissue in the genital organs.

IV.—THE THEORY OF PERSISTENT THYMUS.

The fourth theory, originally proposed, and mostly supported by Klebs, has of late been little considered, for it

has been found that persistence of the thymus body is far from being a constant accompaniment of the disease. In those cases where the thymus is absent, we certainly cannot look on this body as the originating point of the vascular overgrowth which seems to be a regular feature in all cases of acromegalia.

In autopsies performed during the past two years, comprising a considerable variety of morbid conditions, I have found persistence of the thymus body in five per cent of the cases.

V.—THE THEORY OF THE THYROID GLAND.

The compensatory relations between the thyroid and pituitary bodies has lead to some confusion in interpreting the relations of lesions of the former in acromegalia. There seems to be no sound basis for regarding thyroid lesions as causal factors in acromegalia. Thyroid lesions of any nature, existing alone and unassociated with a lesion of the pituitary body, never induce acromegalia. The various degrees of hypertrophy and atrophy of the thyroid gland reported in acromegalia in all probability fall within the range of variations in size which are found very commonly in autopsies under a great variety of conditions and are of no particular significance in having produced symptoms during life. It is difficult to interpret these minor degrees of atrophy and hypertrophy of the thyroid gland in acromegalia other than merely coincident features. The gland is also frequently reported perfectly normal.

If, however, in acromegalia, the thyroid lesions should assume the character of hyperplasia, the acromegalic phenomena would be complicated by the addition of the symptoms of Graves' disease. On the other hand, should atrophy of the gland occur beyond a certain critical stage,

as an accidental complication in acromegalia, the manifestations of myxœdema are engrafted on the original malady. Solis-Cohen records a case in which acromegalia and myxœdema occurred together.

Lesions of the thyroid gland in acromegalia then are to be considered as secondary or coincident phenomena. The compensatory relations of the thyroid and pituitary bodies in regard to acromegalia will receive mention later.

The supposition that changes in members of the ductless gland system other than the pituitary are intimately related to the morbid process in acromegalia merits some consideration, for although in the thyroid gland, for instance, considerable degrees of atrophy and hypertrophy may exist in an otherwise healthy individual without exciting symptoms, it does not follow that the same conditions might not produce profound disturbances in an individual afflicted with acromegalia. If minor degrees of atrophy and hypertrophy of the ductless glands do become significant when occurring in acromegalia, *we must consider them secondary and complicating factors in the disease and at present they must give way to the more important task, the effort to clear away the obscurity of the nature of the prime and essential factor of the malady in the pre-hypophyseal lesion.* Until this latter problem can be clearly answered, we can hardly expect to intelligently take up the questions of the subsidiary complicating and modifying components of acromegalia, such as the influence of changes in the congeners of the hypophysis in the ductless gland system.

These five theories, still current among the explanations of acromegalia, are hanging over and obscuring the true problem like a veil and we have reviewed them here *for the*

express purpose of showing their inadequacy and of urging their final dismissal.

Each in its turn has been a stimulus and guide in the study of the malady and each has been tested and found wanting in the light of the very facts uncovered in the effort to prove them. They have served a purpose but are now only encumbrances to the further progress of our knowledge of the disease, tending to hide the main issue and hinder a determinate purposive examination of the crucial facts, especially in pathological anatomy and physiology.

Along with these theories we must also dismiss those indefinite terms which so vaguely identify the essential proximate cause of acromegalia, namely, "tumors," "enlargements," and "disease" of the pituitary body. This may at first seem paradoxical, for the idea has quite firmly gained ground that acromegalia is causally associated with any one of the great variety of lesions of the pituitary body included under these terms. Quite true these phrases do include the essential factor in the induction of acromegalia, but they also include a number of other lesions which have no causal relation to the malady. Hence the pathogenesis of acromegalia is full of confusion. We shall use these terms, however, for the express purpose of pointing out how they obscure the whole subject.

It is certainly important to sift out of these confusing and incongruous conditions, comprised under "disease" of the pituitary body the *specific* condition of the prehypophysis inducing acromegalia, and that is the main purpose of this paper. In the next two chapters we can discuss the relations of the pituitary body to acromegalia.

Chapter X.

THE PATHOGENESIS OF ACROMEGALIA.

VI.—DISEASE OF THE PITUITARY BODY IN ACROMEGALIA.

Disease of the pituitary body has been found so constantly associated with acromegalia, and the changes have been of so striking and unusual a nature as to early attract attention to the possible rôle of this body in the production of the disease. Marie, in his original monograph, first called attention to this possibility and subsequent workers have, for the greater part, agreed on the probable causative relation of disease of this body to acromegalia. The almost absolute occurrence of lesions in the pituitary body in the malady, and the nature of the changes reported, have already been considered under the pathology of the hypophysis cerebri. Though the diseased pituitary body is now generally accepted as a causative agent in acromegalia, Striimpel in a recent article holds that, while tumor formation of the prehypophysis is a regular lesion in the disease, he is inclined to look on it as simply a coordinate feature bearing no causal relation.

Unfortunately the great variety of lesions comprised in the term "disease of the pituitary body" seem to have been indiscriminately regarded as exciting causes of acromegalia. Thus "enlargements," "hyperplasias," "hypertrophies," "cystic" and other degenerations, atrophic conditions, and tumors, such as round-celled and spindle-celled sarcomata, glio-sarcomata, lymphomata, lympho-sarcomata and adenomata have all been recorded under these vague terms of "enlargement" and "disease" of the pituitary body and in these guises have been assigned the rôle of exciting causes of acromegalia.

The difficulty of reconciling such diametrically opposed

conditions in framing a theory of acromegalia based upon *function* of the gland needs no elaboration. In this and the next chapter we shall endeavor to show that with the exception of a single process in the *pre*-hypophysis—increase of the cells and function coincident with hyperplasia or adenoma—all these various lesions may be eliminated from the pathogenesis of acromegalia.

A brief review of the current knowledge of the comparative anatomy, embryology, histology, and physiology of the pituitary gland will be of service before continuing the subject.

*Comparative Anatomy of the Hypophysis.**—Andriezen has traced the pituitary body as far as amphioxus. In the larval amphioxus he finds the analogue of the pituitary body in the subneural gland which he describes as composed of three parts: 1. "An anterior glandular secreting organ;" 2. "A water-vascular tube lined with ciliated epithelium and connecting the buccal cavities with the ventricles and the rest of the neural cavities;" 3. "A posterior sensitive nervous lobe." The anterior lobe of the subneural gland is the forerunner of the anterior lobe of the hypophysis in the higher vertebrates and has a secretory function. It is constructed on the type of a gland possessing a main duct with many branches extending to acini and lobules composed of epithelial cells with secretory structure. The secretion of this protal anterior lobe of the hypophysis passing in to the water-vascular stream flows into the central nervous system and evidently seems to be concerned with the metabolism of the nervous tissues.

* Inserted during revision of proofs. This is taken from Blair's abstract of Andriezen's researches on the "evolution of the pituitary body" presented before the British Medical Association, 1893. *Journal of Mental Science*, XLV, No. 189.

The comparative anatomy of the pituitary body has also been investigated by Hertwig, V. Kupffer, Saint Rénny and others.

This relation of the secretion of the anterior lobe to the nervous system in the lowermost vertebrates is extremely interesting, but it is questionable if this relation is maintained during the evolution of the gland into the hypophysis of the higher vertebrates. Undoubtedly this function of the gland is lost or becomes radically changed in the higher vertebrates. In all forms above larval acraniates and ammocoetes the water-vascular tube and posterior nervous lobe become obliterated. In the higher vertebrates the water-vascular system is superseded by the blood vascular system and the duct of the protal pituitary gland becomes useless and is closed. The secretion continues although the duct is closed; it is internal and makes its way into the blood-vascular system instead of the water-vascular tube.

Embryology.—The pituitary body develops in two separate portions; the anterior or glandular part is formed by a budding upwards of a diverticulum of the buccal epiblast. This epiblastic invagination, known as Rathke's pouch, is met by a downward growth from the second cerebral vesicle, which ultimately forms the posterior or so-called neural lobe and the infundibulum. These two diverticula become enveloped in the same vascular capsule, but they remain permanently distinct from each other. As the anterior glandular lobe becomes constricted off from the invaginated pouch, a portion of the enclosed cavity sometimes remains as an open space or ventricle. In the human adult, however, this cavity usually becomes obliterated.

Histology.—The structure of the posterior or neural lobe needs no special consideration in connection with acromegalia for the essential pathological process of acromegalia is induced by changes in the active functionating

portion of the gland or prehypophysis and in this part only.

In the early phylogenetic stages we have seen that the structure of the prehypophysis is that of a typical racemose gland. In later periods of evolution the typical glandular structure becomes changed, dependent on distinct modification in the character of the function. With the disappearance of the water-vascular system, the mechanism of the gland becomes altered from the external to the internal type of secretion. The ducts disappear and the secretion is absorbed through the lymph channels, or more probably taken directly into the blood vessels. Following this change in the function of the prehypophysis, the structure departs from that of the typical compound gland to the less typical glandular structure of the ductless glands, and is characterized by the mechanism of so-called "internal secretion." Accordingly the alveoli of the prehypophysis, enveloped in a highly vascular connective tissue capsule, are not at all distinct and are very irregularly arranged.

Between these granular acini are found numerous blood vessels, mostly of the capillary type, made up of a single endothelial coat with a small amount of connective tissue adventitia which also contributes the framework of the glandular structure. This great vascularity of the gland has been frequently noted and probably indicates that the internal secretion of the gland is taken up by blood vessels directly.

The acini of the gland are lined by two varieties of epithelial cells, which although much alike in size, shape and distribution are still different in staining reactions and in the minute structure of the cytoplasm. The cells of the first variety are of the low columnar type with rela-

tively large oval nuclei situated near the attached border, and a clear or but slightly granular cytoplasm. These are known as the *chief cells* and include the majority of the pituitary gland cells. The second variety of cells are differentiated by their staining reaction and the granular condition of the protoplasm rather than by gross morphological features or peculiarities in distribution. These cells of the second class, the *chromophilic cells*, are, as a rule, slightly larger than the chief cells; they are usually oval in shape, though naturally this depends somewhat on the location and arrangement. The relatively large oval nucleus is ordinarily centrally situated. The cytoplasm of the chromophilic cells is very coarsely granular, and, apparently, it is this granulation which gives rise to the characteristic staining reactions of the cells, the protoplasm of which shows, in general, an acidophilic affinity, taking eosin in the hæmatoxylin-eosin method, picric acid in the various dyes containing this chemical, and the blue in Merkel's stain. The chief cells, on the contrary, stain a faint lilac with the hæmatoxylin-eosin, refuse picric acid and react to the carmine in Merkel's dye. The distribution of the two sets of cells in the formation of alveoli does not conform to any regular plan. Apparently entire alveoli may be exclusively composed of either type of cell. The alveoli composed of chromophilic cells are usually larger and more irregular in shape than those formed of the chief cells. Other alveoli while mainly composed of chief cells also contain chromphilic cells occurring singly or in groups of two and three.

It is thought by some, that the chromophilic or granular cell, simply represents a functionating form of the ordinary epithelial cell of the prehypophysis; this belief, however, is not generally accepted. The chromophilic

cells, and the acini made up of them, are found in greatest number in the peripheral portions of the gland, while the centre is made up mostly of alveoli formed of the chief cells.

Just at the juncture of the anterior and posterior lobes are usually found a few large acini containing a colloid material very similar in appearance to the alveoli of the thyroid gland. These are lined by a single layer of cuboidal, or flattened epithelial cells, which appear to have been originally of the chromophilic type. (Schönemann). These colloid areas are also found in various other portions of the prehypophysis, frequently in large numbers. Areas of granular debris, usually centrally situated, are also of common occurrence.

Although the prehypophysis is commonly classed as an example of a ductless gland, Haller has described an imperfect system of ducts opening into the space between the dura and pia mater. This fact probably receives its proper valuation in being interpreted as a persistence or reminiscence of the ancient ducts of the precursor of the hypophysis, the subneural gland of the larval acraniates. Viewed in such a light, the existence of a rudimentary system of ducts is of no particular significance except as an atavistic revival of an archaic structure and is probably of rare and exceptional occurrence. And it is probably for this reason Haller's observation has not been generally corroborated.

Physiology.—We have very little positive knowledge of the physiology of the hypophysis.

Extirpation of the gland has been successfully performed by several observers, but the reports of the resulting symptoms have been of a very contradictory character. In all of the experiments, we must bear in mind the

severity of the operation and the symptoms of derangement which this in itself would perhaps produce. The experiments of Vassale and Sacchi have probably been the most successful; one of their animals, a dog, outlived the operation for the space of one year. They report as the manifestations following the operation: apathy, somnolence, weakened gait, dyspnœa, anorexia, lowered temperature, fibrillary tremors and tonic and clonic contractions of the muscles. Horsley, on the contrary, found no symptoms of consequence following the operation.

The relation existing between the prehypophysis and the thyroid gland has been definitely proven by Rogowitsch, Stieda, Gley and others, all of whom find a compensatory hypertrophy taking place in the prehypophysis when the thyroid is removed.

Experimental injection of extracts of the pituitary body has been quite extensively studied, but these researches have been disappointing from the meagre and contradictory nature of the results. Szymonowicz reports, in his series of experiments, a slight fall of blood-pressure with a quickened action of the heart, and he concludes, in general, that the action of the extract is opposite to that produced by absorption of the extract of the adrenal body. Oliver and Shaeffer, on the other hand, find effects similar to those produced by adrenal extract, the blood pressure being then increased and the heart action augmented. Finally, Howell has recently reported practically no result following similar experiments conducted with extracts of the prehypophysis, though he does obtain reactions from injection of extracts of the posterior lobe. The great objection to the worth of these experiments, in my opinion, is that they have not been

carried on over a sufficient length of time. The reason these researches prove so inconclusive is that the injections should be given over a period of months before we should expect to find effects from the action of the pituitary secretion. Extracts of the hypophysis used therapeutically have likewise shown no effects which can be looked upon as throwing any definite light on the physiology of the organ.

In conclusion, though physiological research has practically failed to establish or define the rôle which the hypophysis plays in the animal economy, yet, from the variations found in its structure in disease and from the study of the pathological condition of the gland in acromegalia we gain a considerable insight or at least a clue to the normal physiological activity of the organ. It appears from the study of acromegalia that the gland furnishes a secretion which is very intimately related to the overgrowth of connective tissue; that is, the secretion contains some active principle which acts directly on the connective tissue.

From the fact that tumors of the pituitary body may attain considerable volume, the question naturally arises as to the origin of acromegalia through pressure on the structures at the base of the brain in the pituitary region and not from disease of the hypophysis in itself.

This supposition is wholly disproven by clear evidence of tumors of this region occurring quite frequently with absolutely none of the characteristic symptoms of acromegalia. Through the kindness of Dr. D. H. McAlpin, I have recently been able to study a case in which the posterior lobe of the hypophysis was the point of

origin of a spindle cell sarcoma measuring 6 cm. in diameter and almost completely destroying, in its growth, the entire pituitary body. It was so located as to occupy precisely the same space as an enlarged pituitary body; yet absolutely no evidences of acromegalia were manifested by the case. Boyce and Beadles have collected a considerable number of cases of tumor of the hypophysis, some of large size, but associated with no symptoms of the disease. Hughes of Philadelphia has recently recorded two similar cases. From these instances, of which many more examples are recorded, it appears perfectly certain that the pressure exerted by the enlarged pituitary on the cerebral base is not in any way causative of acromegalia.

We can now appreciate the contradictions involved in the indiscriminate consideration of the various lesions, grouped as disease of the pituitary body, as proximate causes of acromegalia, and clear the way for the acceptance of a single specific process in the prehypophysis as the basis of the pathogenesis of the disease. Let us analyze these various lesions comprised by the term disease of the pituitary body, adopting as a guide the relations they bear to the function of the gland. It is manifest that the only reliable key to the unraveling of this rather chaotic mass of morphological alterations in the hypophysis obscuring the pathogenesis of acromegalia is on the *basis of function*. This is so because these various lesions of the hypophysis can operate to the production of acromegalia only by coincident changes in the functions of the gland.

If we take as a basis of classifying this heterogeneous collection of hypophyseal lesions, all regarded as proximate causal factors of the malady, the criterion of quantitative

changes in the secretion, the lesions fall into two clearly defined groups. Into one group fall those lesions which accompany diminution or various degrees of suppression of the function of the gland. A second group includes the lesions denoting increase of the function. The first group comprises the lesions, no matter how diverse their morphological character, which induce or accompany atrophic conditions of the gland; in this group, then, fall the various tumors of the pituitary body tending to replace the parenchyma of the prehypophysis, as well as degenerative and destructive lesions of any nature.

The second group, which will be more fully considered in a subsequent chapter, is constituted by those lesions which go hand in hand with an increase of the functionating cells of the prehypophysis, and includes the hyperplasias and adenomas of the prehypophysis,—two lesions indicating the same process; for hyperplasia which has assumed the structural type of a gland is still hyperplasia but by another name,—adenoma.

Having separated the various lesions of the pituitary body supposed to be causally associated with acromegalia, we are now in a position to determine the validity of this relation in each of the two groups. Let us first enquire about the group inducing atrophy of the prehypophysis. Do the neoplasms of the hypophysis, which form the great majority of the acromegalic hypophyseal lesions in the literature, such as sarcoma, replace the gland, diminishing or suppressing its function, and thus give rise to acromegalia? Quite a number of observers have answered this question in the affirmative and it appears that Marie himself was at first in favor of this theory and first formulated it. Rogowitsch, studying the compensatory hypertrophy of the pituitary body after extirpation of the

thyroid gland, expresses the opinion that the function of the prehypophysis is to destroy, remove or transform toxic substances accumulating in the blood, as in the case of the thyroid gland. It may be recalled that prior to Rogowitsch's studies (1889) hardly anything was known about the functions of the hypophysis. According to Rogowitsch's idea the rôle of the prehypophysis in acromegalia would be quite analogous to that of the thyroid gland in myxœdema. Marie and Marinesco give Rogowitsch's theory a prominent place in their articles on acromegalia; at least, one receives the impression that they accept the theory in preference to all other explanations of the nature of the malady.

I think we can say very positively that the supposition of the pituitary gland atrophy and diminution of function as a cause of acromegalia is utterly wrong. It is flatly contradicted by definite and reliable facts. The incontrovertible objection to the atrophy theory lies in the weight of facts like those shown in my examination of McAlpin's case just cited. Here is clear and positive evidence of gradual and almost complete destruction of the entire pituitary body by a sarcomatous growth with no approach to the characteristic acromegalic phenomena. In the series collected by Boyce and Beadles, several similar instances are adduced which also disprove this theory of hypophyseal atrophy.

Experimental evidence also coincides with these facts. The researches of Vassali and Sacchi, of Horsley and others, who succeeded in removing the pituitary gland in some of the lower animals, have not found, in any of these animals osseous or interstitial changes similar to those of acromegalia.

Again, if acromegalia were dependent upon pituitary

atrophy, in the medication, by supplying to the system a substitute for the diminution or deficiency of the normal secretion, we should expect, as in myxœdema, at least some amelioration of the symptoms following the administration of extracts of the gland. It is now, however, generally admitted that such medication meets with no favorable results in acromegalia. Although this latter argument against the atrophy theory is not conclusive it has a certain weight when added to the other objections.

We perceive then that the first group of atrophic lesions of the hypophysis as the proximate cause of acromegalia, are to be regarded with strong suspicion. Indeed, I believe an error must have crept into the interpretation of these atrophic lesions of the hypophysis in acromegalia and led the research and understanding of the nature of the malady astray. We should not take it for granted that this diagnosis of sarcoma of the gland is really correct, even though it seems to carry much weight in applying to a majority of cases examined. In fine, the error lies in the fact that these instances of sarcoma of the hypophysis in acromegalia are not sarcomata at all. In such cases hyperplasia has been mistaken for sarcoma of the gland and in the next chapter I think it will be easy to see that this standpoint is correct.

Chapter XI.

THE PATHOGENESIS OF ACROMEGALIA—(*Continued.*)

VII.—THE SPECIFIC LESION OF INCREASE OF THE PREHYPOPHYSEAL CELLS IN ACROMEGALIA.

This second group of hypophyseal lesions is constituted by hyperplasia and adenoma of the gland, which may be considered as manifestations of a single pathological process—increase of the function and functionating cells of

the prehypophysis. By the process of elimination, in the last chapter the field of pituitary lesions was virtually narrowed down to the second or hyperplastic class of changes, and these are the true and essential lesions in acromegalia. Besides the reasoning from the method of exclusion, there are also positive data supporting this theory, for, in several cases, observers have interpreted the results of their examination of the pituitary changes as hyperplasia or adenoma. These data furnish the key to disentangle the discordant observations and if we adhere to these results the subject seems clear.

Against the view of the increased function and hyperplasia theory, however, stand the observations of the cases of sarcoma and morphologically similar neoplasms of the hypophysis in acromegalia. These observations greatly outweigh in number the instances recorded as hyperplasia and adenoma, and, in fact, constitute the great bulk of evidence in cases examined microscopically.

If we can show, however, that there are good reasons for believing that these instances of sarcoma have been wrongly interpreted and are really examples of hyperplasia, the pathogenesis of acromegalia stands out clearly on a basis of harmonious data. This is not difficult. The mistake of confounding hyperplasia and even adenoma of the gland for sarcoma might be very easily committed indeed. The glandular structure of the hypophysis is rather atypical, its cells are small and rather densely huddled together, and the connective tissue is very scanty. Consequently in an hyperplastic overgrowth the appearance resembles, very closely indeed, a sarcoma of the small round-celled or lympho-sarcomatous type.

I feel quite free to confess that in studying my first case, not having reflected on the nature of the disease, or

sifted the literature, and having no theory to work on except the conventional idea of any lesion, especially neoplasms of the hypophysis, being sufficient as an exciting cause of acromegalia, I considered the enlargement of the pituitary body due to small round-celled sarcoma. My main problem, in harmony with the general work of this Institute, was focused on the nervous system; to determine more definitely to what extent the nervous system was involved in the disease, and to correlate the neural lesions with other morbid changes in the body at large. A second case, however, coming to hand very shortly after the first, fortunately presented so plainly the structure of adenoma of the prehypophysis, that I began to reflect on the concurrent changes in the *function* of the gland. The preliminary induction from this straightforward fact to the idea of the hyperfunction theory, was certainly not difficult to make; and under the guidance of this idea a renewed study of the initial case showed what I had set down as sarcoma to be plainly hyperplasia. A third case turned out the same way. Here again I should have called the hyperplasia sarcoma had it not been for the different trend of thought suggested by the second case. I have had the opportunity of studying sections of the hypophysis from four additional cases of acromegalia, and all of these exhibit increase of the prehypophyseal functionating cells (three of these were diffuse hyperplasia and the other was adenoma).

Furthermore, these so-called sarcomata of the hypophysis in acromegalia are lacking in two rather predominant traits of sarcoma. We should expect evidences of metastasis and comparatively rapid growth, yet both of these characteristics are absent. With the exception of a few cases, the course of acromegalia is notoriously slow,

gradual and chronic, and extends over a number of years. Such a course in the growth of a sarcoma would be a rather striking exception to the rule.

The hypersecretion theory, as far as I am able to learn, was first brought forward by Tamburini, but I feel like stating it much more positively.

Finally, there is a peculiar set of hypertrophies or hyperplasias of the prehypophysis of slight degrees, entirely unassociated with acromegalia. This, however, does not at all conflict with the prehypophyseal hyperplasia theory of acromegalia and is readily explained. This particular group of hypertrophies or hyperplasias of the prehypophysis are of a compensatory nature consecutive to atrophic conditions of the thyroid gland. From Rogowitsch's observations of hypertrophy of the prehypophysis after experimental extirpation of the thyroid gland, we should expect to find this condition in cretinism and myxœdema; and Boyce and Beadles, Hofmeister, Putman report such changes in the prehypophysis in both of these diseases. These observations are further corroborated by Stieda and Marinesco. Such an increase of the function of the prehypophysis is wholly apart from the condition in acromegalia. It is dependent entirely upon atrophic lesions of the thyroid gland; the increased function of the prehypophysis is only relative, supplying a deficiency of the *thyroid secretion*, and does not provide the organism with an actual increase of *prehypophyseal secretion* as in acromegalia. In a series of one hundred and thirty-five autopsies performed during the past year I have noted in several instances the occurrence of a slightly enlarged hypophysis in cases of atrophic conditions of the thyroid gland. This observation, however, of gross conditions is of little value, for I have neglected to record the meas-

urements and weights of the gland. Both of these are subject to such considerable variation in the normal individual that the significance of enlargements of the pituitary body are very difficult to determine even with exact measurements and careful cytological study.

A point of much importance in the acromegalic prehypophyseal hyperplasias is the determination of the increase of the chromophilic cells. These are considered by some observers to represent the active functionating stage of the chief cells. This supposition seems to be supported by the structural analogy which the chromophilic cells bear to other actively functionating gland cells in their distinctly granular characteristics. If this be so, the preponderance of chromophilic cells in hyperplasia and adenoma in acromegalia would coincide with a greater degree of functional activity of the growth. According to this idea an overgrowth of the hypophyseal cells mainly composed of chromophilic cells, might not be accompanied with the grosser degrees of enlargement and still be of great significance in acromegalia. Unfortunately the study of this particular feature has been badly neglected, and altogether the majority of the patho-anatomical researches of the pituitary lesions in acromegalia have been superficial and even careless. For this reason I have deliberately recorded the data of my own cases with what may seem perhaps too elaborate or useless detail in order to reduce ambiguity to a minimum, especially in reference to the nature of the pituitary lesions and thus make the data serviceable for the use of other observers.

Relation of the Increased Pituitary Function to the Connective Tissue Growth.—This can be stated only in the most general terms, for the great laws of patho-

logical growth of connective tissue have yet to be discovered. We may say, provisionally, that the increased secretion of the prehypophysis in acromegalia acts as a direct stimulus to the connective tissue cells and by its persistent action slowly and constantly augments their growth. Whether this takes place in the vessels primarily or in both the vessels and general connective tissue simultaneously is difficult to determine, but the latter supposition seems more probable. The vascular changes and the overgrowth of certain of the mesoblastic structures, such as the bones, periostea, dermal connective tissue, visceral interstitia, go hand in hand, are coincident.

The Relation of the Hypophyseal Hypersecretion to Parenchymatous Degeneration.—This question is also difficult to pronounce upon, as the data at hand are not sufficiently determinate. I believe, however, that the secretion does not act as a degenerative stimulus to the various parenchyma cells. So many complicating and secondary processes may be engrafted on acromegalia that we should be careful to eliminate them before ascribing parenchymatous degeneration to the acromegalic process itself. In a perfectly uncomplicated case, and especially in the earlier stage, I should not expect the changes in the various organs to involve the parenchyma cells directly, but to be confined to the stroma alone. In the later stages of the disease, when a cachectic habit is established, the condition, with respect to parenchyma degeneration, is quite different. Various degrees of parenchymatous degenerations might then well occur from the greatly reduced status of the general nutrition.

This consideration leads us to the question of increase of parenchyma cells indicated by the observations of the

increase of the size of various viscera. These observations must be accepted. The increase of the visceral interstitium alone is not sufficient to account for the collective enlargement of the abdominal viscera, termed splanchomegalia. There is an actual increase of the parenchyma cells of certain organs, as, for instance, the liver and the kidneys. The explanation is, I believe, that this is a compensatory hypertrophy, consecutive to the demand on the function of the organs by the increased general metabolism throughout the whole body and especially in the connective tissues.

The Relation of the Acromegalic Process to the Nervous System.—This was one of the main motives of this research, but it seems to me now that the general impression that acromegalia should be reckoned among the diseases of the nervous system or is accompanied by predominant or uniform psychopathic or neuropathic phenomena* is greatly exaggerated. Acromegalia is a general somatic disease. Of course a great number of nervous and mental diseases are brought about through general somatic disease, but in some conditions the sequence is definite and occurs with more or less uniformity so that the phenomena have a definite range and interdependence; in short, the manifestations are constant and form a symptom-complex occurring with sufficient uniformity to warrant a designation of the phenomena under a collective title or name. This can hardly be said of the nervous or mental phenomena of acromegalia. It seems to me that acromegalia, *per se*, has very little to do with the nervous system. It is quite true that various nervous and mental symptoms are irregularly associated with this dis-

* These terms are used with the meaning attached to them by Van Gieson and Sidis. See Neuron Energy and its Psychomotor Manifestations, ARCHIVES OF NEUROLOGY AND PSYCHOPATHOLOGY, Vol. I, p. 5.

ease, and it is much to be regretted that careful psychopathic methods of examination have not been followed out in the malady, particularly in our own cases. It is questionable, however, whether these symptoms of the nervous system are not to be ascribed to secondary or complicating processes that may be engrafted on acromegalia or follow in its track. In the later cachectic stages of the disease, the liability of involvement of the nervous system becomes less doubtful. Various psychopathic and neuropathic phenomena might then readily be initiated from defective nutrition or accumulation in the body of toxic substances.

Thus the instances of insanity recorded with acromegalia might depend upon the terminal phases of acromegalia as well as upon complicating or secondary factors. Two conditions, however, are the direct outcome of the acromegalic process and would tend to arouse nervous or mental phenomena in the disease quite constantly. These are the tendency toward connective tissue proliferation in the peripheral nerves, and the lesions of the blood vessels of the nervous system. In the former is one of the explanations of the neuralgic pains, and possibly the acroparæsthesiæ. In the latter is a source of various mental nervous phenomena both functional and organic. The rather frequent occurrence of syringo-myelia with acromegalia receives its probable explanation in the fact that the residual spongioblastic tissue in the region of the central tubular gray matter reacts like connective tissue elsewhere in the body under the stimulus of this increased pituitary secretion and undergoes hyperplasia. Erythromelalgia has been recorded in several cases of acromegalia. Weir Mitchell and Spiller, Sachs and Wiener*

*May meeting of the New York Neurological Society, 1899. Inserted during revision of the proofs.

have studied the pathogenesis of this phenomenon and show that it is dependent upon severe degrees of obliterating endarteritis of the arteries of the foot. The occurrence of erythromelalgia in acromegalia is corroborative of these observations, for in the rather universal involvement of the vascular system we should expect that in certain cases the vessels of the extremities might undergo the more severe degrees of obliterating endarteritis causing the erythromelalgic phenomena.

Chapter XII.

DIAGNOSIS.

The diagnosis of acromegalia, in well marked cases, presents few difficulties. One acquainted with the condition is often able to make the diagnosis at a mere glance on seeing the patient in the hospital ward, or even across the street. Often the general appearance of the patient, or the picture presented by the disease as a whole, gives one a more vivid and accurate "impression" of the malady than a close and detailed examination will verify. This is especially true, where too much reliance is placed on the value of increased measurements, for in cases not yet well advanced, these variations are so slight that they are often still within the range of normal.

Usually the first point to attract the clinician's attention to the disease is the bilateral enlargement of the extremities and this is often so characteristic that a provisional diagnosis is at once arrived at. The enlarged head and face are generally next noted. Here, where the changes are moderately advanced, the long oval face, the prognathism, macroglossia, everted and thickened lips, the hypertrophied nose and prominent malar bones,

together with the olive pigmentations of the skin so often present, give an unmistakable picture of one condition—acromegalia.

The gigantic proportions of the body and the humped back are, also, often very striking factors in the general consideration of the physical evidence of the disease. Usually, some of these changes have already been noted by the patient, or, at least, he recalls that he now requires larger sized articles of clothing, as gloves, shoes and hats, than formerly. On inquiry the patient complains more or less of pains, or uncomfortable sensations in the head; of neuralgic pains in the face or extremities and often of polydipsia, polyuria or hyperidrosis.

The ocular symptoms arising from the growth of an ordinary tumor of the base of the brain in the pituitary region should not be difficult to differentiate from the main manifestations of acromegalia. Hyperplasia of the prehypophysis large enough to produce pressure on the optic nerves is well advanced and the acromegalic physical signs would be correspondingly manifest.

Neuralgias, migraines and uncomfortable sensations in the head are present in both conditions, but the case of simple tumor is easily differentiated by the lack of the associated enlarged extremities and the characteristic abnormalities of the bones of the face and head. Never, in simple brain tumor, do we find the general disease picture of acromegalia.

The eyesight is often deficient and troublesome. Menstrual and sexual irregularities are discovered on further questioning, and, frequently, a general progressive muscular weakness has been noticed by the patient, who usually adds, often voluntarily, that the appetite is excessive. It must not be forgotten that any one or more of these

manifestations may be wanting, and it cannot be impressed too strongly, that ofttimes where the more characteristic physical signs of the disease are poorly shown or are masked by other pathological conditions, the diagnosis of acromegalia must rest on the *general picture* of the manifestations taken collectively, in perspective.

Intercurrent diseases of every description may be present and, sometimes, are of such nature as to greatly confuse the chief diagnostic points.

Physical examination may be entirely negative, but usually the liver and spleen are enlarged and the latter may be even palpable. The heart may be hypertrophied, and, although its action is generally regular, the pulse has a tendency to be soft and compressible. The electrical reactions are not characteristic. Ophthalmic examinations often yield evidences of pressure on the optic chiasm, and narrowing of the field of vision is common. The urine is usually abundant and often contains considerable sugar together with traces of albumen, casts and renal epithelium.

While, taken as a whole, the disease-picture presented in acromegalia is quite characteristic and easy of diagnosis, often a detailed study is more or less unsatisfactory on account of the numerous variations in the minor signs and symptoms shown. The differential diagnosis presents the greatest difficulties, since the disease closely resembles, in many respects, certain other conditions which are liable to be mistaken for acromegalia, or *vice versa*.

Gigantism is a condition very closely allied to acromegalia, as the studies of Dana, Hutchinson and numerous others have shown. Indeed, if Marie's statement that "acromegalia is gigantism of the adult; gigantism is acromegalia of the adolescent," may be generally accepted,

the acromegalic manifestations follow two types, depending upon the age when the patient is affected. In young individuals the gigantic type occurs; in adults the ordinary type of acromegalia results. The two types may be differentiated in the contrast of symmetrical and more or less universal increased growth in gigantism, against the bilateral enlargement of the extremities and the characteristic physiognomy in acromegalia. A further consideration of the relations of gigantism to acromegalia is given in Chapter XIV in the discussion of the cases of Joffroy, Schütte, Brissaud and Meige, Buday and Janesco.

It appears that while the glycosuria, which is so commonly found in acromegalia, is secondary to the general disease, yet it happens quite commonly that cases of acromegalia are mistaken for those of simple diabetes, and indeed, this error is not surprising, for, as is well known, diabetes is quite prone to attack those of the large stature and heavy build. The urine in both conditions frequently contains large quantities of sugar; the somnolence in acromegalia as well as the polyphagia and polydipsia are probably symptoms of the associated diabetes. The muscular deficiency and skin lesions are common to both processes. The differential diagnosis between these two conditions must rest on the gross anatomical lesions characteristic in acromegalia; on the progressive enlargement of the extremities; the ocular disturbances, and neuralgia, none of which are ordinarily present in simple diabetes.

Still another manifestation of acromegalia which often causes question in the differential diagnosis, is the suppression of the menstrual function in female patients. This amenorrhœa, in conjunction with the disordered mentality of the patient, the various neuralgias and

other symptoms of the disease is ofttimes mistaken, not only by the patient, but also by the medical man, for those obscure and ill-defined symptoms which frequently accompany the establishment of the menopause; hence it becomes necessary that the observation of the patient should, in these particular cases, be especially careful. Here again the principal differential points are to be found in the altered physiognomy, indicative of acromegalia, and the progression of these peculiarities renders diagnosis certain.

Occasionally, the diffuse pains throughout the body, especially in the bones and joints, give rise to a diagnosis of rheumatism and the bony changes, which begin to take place in the early stages of acromegalia, may quite easily be mistaken for a rheumatic arthritis. But if the case remains under observation for a short time, acromegalic characteristics soon become sufficiently evident to make differentiation quite positive.

It sometimes happens that early cases of acromegalia present indefinite general neuralgias and sensory disturbances which may serve to confuse the malady with tabes dorsalis. In simple acromegalia, however, the pains are chiefly confined to the head and, when present at the waist line or in the extremities, they are very rarely so severe, as the excruciating, darting pains of tabes. The loss of reflexes in posterior spinal sclerosis is another quite characteristic differential point. But where acromegalia is combined with disease of the posterior columns, as in a case reported by Nonne, differential diagnosis is by no means easy.

Syringomyelia also presents some manifestations which are likely to prove somewhat confusing. The atrophies found in syringomyelia, unless they follow the strict

progressive type, which is rather more uncommon than otherwise, may be taken for the atrophies of acromegalia. The sensory disturbances are sometimes confusing, but when temperature and pain sense are defective, and touch still remains, as is the case in typical syringomyelia, the differentiation becomes absolute. The changes which are sometimes seen in the hands in syringomyelia are somewhat similar to those of acromegalia, though the atrophies are much more prominent in the first mentioned condition. In pure syringomyelia, we have no indications of intra-cerebral tumor, or of ocular disease, which are almost constant manifestations of acromegalia, while indications of a progressive cord disorder are the most apparent manifestations of the condition.

From about the same standpoint acromegalia must be differentiated from the various myopathies, in which either hypertrophy or atrophy of the voluntary muscles take place, and, for the same reason, various cord diseases which produce muscular atrophies, must be distinguished from the somewhat similar atrophies of acromegalia; however, these diseases are usually quite easily excluded by the bony changes and altered physiognomy of acromegalia. The skin changes found in the above diseases, as well as in several other conditions, as elephantiasis and adiposus dolorosa resemble, in some respects, very strongly the dermal lesions of acromegalia, which is, however, easily separated from such conditions by the general disease manifestations.

Characteristic as are the skeletal and external physical changes in well marked acromegalics, yet they are strongly simulated by some other diseased conditions. That which most closely resembles the acromegalic type, is found in the "osteoarthropathie hypertrophiante" of

Marie, a condition, which is believed to be secondary to, and dependent on, extensive disease of the lungs, whereby the function of these organs becomes seriously interfered with. Hence, in this disease, we find primarily extensive pulmonic lesions usually of a chronic nature, as interstitial pulmonitis, bronchitis, empyema, chronic tuberculosis or new growths of the lungs. The face in "osteoarthropathie hypertrophiante" shows little, or no change, and the hypertrophy and prognathism of the inferior maxilla, so prominent in acromegalia, is wholly absent. The hands and fingers, in the secondary condition, while they are quite striking, differ in many essential ways from the same members in acromegalia and instead of being of the classical "sausage shape," the ends are clubbed. The nails also differ from those of acromegalia, being large, thick and broad. The hands in this secondary ostitis, are usually irregularly deformed, and do not present the more or less symmetrical enlargement found in acromegalia. Finally, we do not find the indications of intra-cerebral tumor which are almost constant in acromegalia.

Leontiasis ossea also presents some features which, at first sight, might be mistaken for acromegalia. In this condition, however, the skull appears to be the only portion of the skeleton involved and here the changes are quite different from those of acromegalia. Instead of characteristic physiognomy of acromegalia, we find the features flattened and obliterated by a diffuse hypertrophy of the bones or by irregular masses of bony deposit, thus presenting an altogether different picture from the symmetrical hypertrophies of acromegalia.

The enlargement in adiposus dolorosa (Dercum) is very easily distinguished, since the increase in size is entirely due to a deposit of fat and no bony changes whatsoever are present.

Arthritis deformans can be readily differentiated by its rather characteristic deformities.

Numerous other conditions exist, in which we find enlargement of the extremities and these might, for a time, be mistaken for the early changes of acromegalia, but we should bear in mind that in acromegalia, and in acromegalia alone, we find the combined condition of symmetrical bilateral enlargement, involving both the soft and bony tissues, following the normal lines of growth, and accompanied by symptoms indicative of enlargement of the pituitary body.

In the early stages of acromegalia, before the appearance of the body has been much changed, it is often very difficult to differentiate the oncoming disease from certain other nutritive disorders, notably myxœdema, but, as the disease progresses, the differential points become more and more evident. One especial point of difference is the absence of bony changes in myxœdema; the increase in size and the deformities result entirely from disease of the soft parts, hence, we have absent in this disease, for instance, the very characteristic enlarged and prognathic lower jaw of acromegalia. The skin in myxœdema also differs very appreciably from that in acromegalia, where we find so many evidences of distrophy. These points and many others, if carefully considered, serve to differentiate the conditions, but perhaps the most conclusive point of all is found in that thyroid medication produces marked amelioration in myxœdema, while in acromegalia it has little or no effect. Cretins may be distinguished from youthful acromegalics by the fact that, in the first mentioned instance, growth is stunted, while youthful acromegalics are usually of the gigantic type.

Sternberg states that patients of a lymphatic constitu-

tion, combined with rachitis, sometimes present abnormalities, which resemble, to a greater or less degree, those of acromegalia and which are apparently only to be distinguished from it by the progress of the disease.

We find some important points of similarity in the pathology of acromegalia and Basedow's disease. Often in acromegalia there is thyroid hypertrophy, and, though generally of less degree than in well marked cases of Basedow's disease, still it is of the same nature. Hence, it does not seem strange that more or less clinical similarity should also exist, and such is the case. When acromegalia has become fully developed, the unmistakable anatomical changes render differential diagnosis easy, but, in the incipient stage of acromegalia, the clinical pictures are quite similar. Exophthalmus, one of the cardinal symptoms of Basedow's disease, is also quite often found in acromegalia, but here it is almost invariably associated with considerable destruction of vision, which is rarely the case in Basedow's disease. The mental symptoms in both diseases are quite similar in some respects, as are also the skin changes. The great acceleration of heart action in Basedow's disease, which is rarely present in acromegalia, is a very important differential point. In Basedow's disease, contrasting with the somnolence of acromegalia, we have, among other symptoms, hyper-nervous tension, manifested by extreme wakefulness. In acromegalia, tremors are rare and when present are found only in the well developed cases where diagnosis is simple; but in exophthalmic goitre tremors are common and develop early. As the case remains longer under observation, the abnormalities of growth which take place in acromegalia soon place the diagnosis from Basedow's disease beyond question.

In considering all these conditions, we should always remember that these diseases, or any other, may be found in conjunction with acromegalia. In conclusion, while well marked acromegalia is a disease presenting, in general, few difficulties of diagnosis, many of its characteristics are closely simulated by other and, in some instances, probably closely allied conditions. Diagnosis is often confused by the co-existence of other maladies. Some of these—such as syringomyelia, tabes or myxœdema—very seriously obscure both the symptomatic and the physical pictures of the disease. Finally, it must again be emphasized that oftentimes the diagnosis must rest, not on any special series of signs or symptoms, but on a broad, comprehensive and general view of the onset, symptoms, physical signs, abnormalities of the features and, perhaps most important of all, on the *progression*.

Chapter XIII.

THE PROGNOSIS AND TREATMENT.

The prognosis, even in uncomplicated acromegalia, is always bad. No cases of complete recovery are reported, though in many cases, under favorable conditions, the progress of the disease appears to have been arrested; in these instances the patient may live out the natural term of life. Complications by other disease, of course, render the prognosis worse. In general, it may be said that the best prognosis as to life is to be made in those cases where the disease develops after or during middle life, while those cases which manifest the disease shortly after puberty or in early adult life are apt to run the more rapid course.

In making a prognosis, the clinician should always

carefully consider the surroundings and character of the patient, as well as the response to treatment and hygiene.

Death usually results from some intercurrent disease, commonly nephritis or diabetic coma, complications which are, no doubt, due primarily to changes induced in the kidneys and pancreas by the acromegalic process.

The treatment of acromegalia can be best considered under three heads, *Symptomatic*, *General* and *Specific*.

Symptomatic.—Naturally, the attention of the therapeutist is first attracted to the symptomatic aspects of the disease, since the patient comes complaining of the symptoms and not usually as yet aware of the anatomical changes which later become so characteristic of the disease. On account of the particularly distressing nature of some of these symptoms, it is often imperative that more or less relief be afforded at once.

Perhaps the most common, as well as the most painful, of all the symptoms, is the neuralgia of the branches of the trifacial nerve, and the headaches. Since the disease is almost certainly to be of long duration, it is well to refrain from the use of morphine, as long as practicable, or, if necessary to use it, as is sometimes found to be the case, the drug should be employed in as small doses as possible. Probably the most reliable agents, aside from opium, which we may use for relieving these symptoms, are the various members of the coal tar group, and among the most potent of these are salol and phenacetin. It is often beneficial to vary the drug frequently when tolerance to those in use appears to be becoming established. We frequently obtain benefit from the use of trional or similar drugs, in small doses. The bromides often give great relief. These same measures will usually relieve

the body and muscular pains of which complaint is often made.

The ocular symptoms are sometimes among the most aggravating features, and, frequently, these also yield, in some degree, to properly directed symptomatic treatment. Glasses sometimes give more or less relief in eye strain; prisms may correct muscular insufficiency, and ordinary lotions relieve the blepharitis which is, at times, very annoying.

The somnolence may occasionally be combated by tea and coffee or their active principles, but the results are not very satisfactory. (Dercum).

Glycosuria is to be met by proper diet with perhaps the use of codeine and arsenite of sodium.

General.—In the general treatment of acromegalia much can be accomplished. Osborne states that tonics, combined with rest, generally produce an amelioration of symptoms and frequently bring the disease to a standstill. Such fortunate results, however, are not common. Sternberg recommends the use of iodide of potassium, alone or together with mercurial inunctions, and reports good results following this treatment, even though the cases be non-syphilitic. Schlesinger has also found benefit from the use of mercurial inunctions. Banks reports mental improvement under potassium and sodium bromides. Dercum, Campbell and others have used arsenic with good results.

Caton and Paul have, as a last resort, attempted relief by removal of the pituitary body but with fatal results. It seems only just to say that in their case, the operation was hardly given a fair chance, as the patient was in a very low condition before operation was resorted to. Keen has resected the peripheral nerves which were the

seat of the most annoying neuralgic pains. Lynn-Thomas have obtained relief from the pressure symptoms, due to the growth of the tumor, by removal of a segment of the calvarium, but, in the ordinary case, the pressure symptoms are hardly severe enough to demand this measure.

The most beneficial treatments in acromegalia, however, are those which are discovered by a careful study of each individual case but these must, in great part, be determined by the social and financial condition of the patient, as well as by the resources at the command of the physician. The mind should be diverted to outside interests, as often the patient becomes introspective and morose. Travel and social intercourse often serve to keep the patient's mind off himself, but in other cases these avenues are closed by the sensitiveness of the patient to the exposure of his deformities. Unfortunately, the failing eyesight often deprives the acromegalic of some of the most fruitful means of mental occupation. Where possible, it is well for the patient to keep up his usual lines of work, but overwork or business worry should be carefully guarded against. Moderate physical exercise, preferably in the open air, should be encouraged, and this may, oftentimes, be efficaciously supplemented by massage, Swedish movements and electrical treatment. Hydrotheraphy can be utilized with good effect. All these means serve, not only to actually benefit the patient physically, but by diverting the mind they often remove, to some extent, the melancholic tendencies sometimes present, and at least give the patient mental rest in the assurance that something is being done for him.

Under the heading of specific treatment of acromegalia are found the most interesting problems in the thera-

peutics of the disease and, at the same time, from a curative standpoint, the most disappointing results.

Working on the theory of functional destruction of the pituitary body, Marinesco, Fraenkel, Mendel, Dodgson, Schultz and numerous others, have employed extracts of the pituitary body in the treatment of the disease. Since other measures were used at the same time, it is impossible to draw any accurate conclusions from the results of these experiments, but the general concensus of opinion of those who have used this extract, is that it fails to produce beneficial results in acromegalia.

On account of the brilliant results attained in myxœdema following thyroid medication, it seems natural that this same agent should be employed in the somewhat allied condition of acromegalia. Then, too, the almost constant abnormalities found in the thyroid in acromegalia as well as myxœdema has, apparently, furnished a basis for this treatment. Consequently various preparations of thyroid have been very extensively employed in the treatment; but, here the reports are at wide variance. Putnam, Parsons, Bromell and Cohen have found benefit following the treatment, but Benson, Fraenkel and Hagelstamm have reported the condition as made worse rather than better. I have recently seen a case, in which some good result seems to have followed thyroid medication. Pausini also records a case with subjective improvement under this treatment. Osler states that he obtained no results—either good or bad from thyroid treatment. Dinke reports good effects following treatment with mixed thyroid and pituitary extracts. Disappointing as these results are, they are but confirmatory of the prehypophyseal hypersecretion theory.

From a résumé of the treatment of acromegalia, it then

appears that the best measures of which we are now possessed for the alleviation of the condition, are those directed to symptomatic relief and to betterment of the general conditions surrounding the patient and that specific treatment has but little, if any, direct effect on the disease itself.

Chapter XIV.

REVIEW OF CURRENT LITERATURE.

Since the completion of this paper, the literature has been unusually rich in reports of cases of acromegalia and several valuable studies have appeared contributing in no small degree to our further knowledge of acromegalia. Though unable to obtain all, we have secured the greater number of these articles.

Bearing on the etiologic relation of heredity, one of the most interesting cases in this recent literature is that of Schwoner, in which both mother and daughter were affected by the disease, and though it is not certain that the father was likewise afflicted, he was known to have been more than ordinarily large. Of course from a single case no conclusions can be drawn, but its thoroughly authenticated occurrence renders the instance well worthy of our consideration, especially since we know that the closely allied condition of gigantism is often hereditary. It is none the less equally certain, according to our present knowledge, that a history of heredity is as rare in acromegalia as it is common in gigantism.

Joffroy has recorded in a most thorough manner a case which was under his immediate observation for a long period of time. He is able to accurately fix the time

of onset of the malady and states that no evidences of this disease were present up to the fifty-third year. Although acromegalia eventually became very pronounced, gigantism was not present. We entirely agree with Joffroy, that when persons not yet fully grown are affected by acromegalia they become giants, while those who have already achieved their full stature before the onset of the disease are not usually rendered morbidly gigantic.

Schütte, in a concise but comprehensive digest, now looks on acromegalia as a secondary disease which is very prone to attack giants; he, however, draws attention to the fact that the enlargement of the disease nearly always follows a normal type, which it exaggerates. This is a point which we also have emphasized.

Brissaud and Meige, in reporting two cases of gigantism following acromegalia, conclude that the conditions are only variations of one and the same process. Ponfick, Huebner and Gerhardt have presented a case of probable acromegalic gigantism in a child of four years. This is one of the youngest cases on record.

One of the most careful and complete reports in the recent literature is that of Buday and Janesco. Their case occurred in a giant and presented several important variations from the usual course of acromegalia. These were chiefly symptomatic, but the authors are inclined to lay so much stress on them that they hesitate to class the case as a true acromegalic. The hands of the patient, though large, did not show the usually characteristic deformity and the authors do not think that the abnormalities of facial configuration were of an absolutely acromegalic type. The photographs of the case, however, seem to represent it as quite typical of the disease. One

of Ponfick's cases seems to have been even more normally formed, though the patient presented the usual symptoms of acromegalia, and at the autopsy a hypophyseal tumor was found, hence he classes his case as one of pathological gigantism, *i. e.*, acromegalia.

None of the recent cases seem to throw any light on the predisposing causes of acromegalia, nor do the latest studies give anything of value on this point. Hinsdale in his monograph, ascribes trauma as a very probable factor in the production of the disease. It is certainly impossible to wholly eliminate this as a predisposing or proximate cause, since a history of traumatism is given by nearly every hospital patient whether acromegalic or otherwise.

Several of these later reports show various irregularities in the symptomatology of acromegalia. Among these Garnier and Sautenoise give an instance in which, contrary to the ordinary course, menstruation persisted. As already stated, the case of Buday and Janesco is to be included among the irregular ones. A tumor of the breast was found in the case of Schwoner; the nature of this tumor, whether primary or secondary, malignant or otherwise, is not stated. As we review the reports of acromegalic cases, however, we can not but be astonished at the constancy and regularity of its chief signs and symptoms; few diseases are so clear and distinctive in their manifestations.

Aside from the monographs of Schütte and Hinsdale, probably the most valuable papers touching on the differential diagnosis of the disease are the communication of Ponfick "Ueber die Beziehungen zwischen Myxodem und Akromegalie," and especially the recent publication of Thayer: "Acromegalia and Hypertrophic Pulmonary Osteo-arthropathy."

All the cases which I have been able to collect from the literature of 1898 show, where autopsies have been obtained, the presence of tumor or enlargement of the hypophysis, or, where only the clinical records are given, by far the majority have distinct symptoms of intracranial growth at the base of the brain. As exceptions to this rule are the clinical cases of Kauffman and of Thompson and Witmer, where none of the recorded symptoms seem to especially indicate such a lesion.

In the cases which came to section, the nature of the pituitary enlargement varies. Ponfick records simple enlargement; Bailey, Hunter, Smyth and Shattuck, describe an adenomatous or hyperplastic tumor. Strümpel and Spiller both believe the growths in their cases to have been round-cell sarcoma, while Johnston and Munro, and Buday and Janesco, also give tumors of a sarcomatous nature. The description in Johnston's and Munro's case is of an alveolar structure which seems to be quite similar to that in the first two cases of the author, while Buday and Janesco specifically state that no indications of malignancy were seen in their specimens and hence they name the growth "adeno-sarcoma." The excellent description of this neoplasm seems to demonstrate that its structure was very like that in our last case.

No new theories of note have been advanced recently as to the causative factor of acromegalia. Hinsdale reviews the most popular theories in a quite elaborate manner, but adds nothing. It is now, one might almost say, universally admitted that the hypophysis plays the leading or exclusive rôle in the pathogenesis of acromegalia, but notwithstanding the indisputable evidence disproving the atrophic or loss of function theory, this theory still seems to be the most generally accepted one.

Recent publications contain several examples of cases in which destruction of the pituitary had taken place, either through neoplasm, as in McAlpin's case, or other causes, without indications of acromegalia. I have laid much stress on this point in the body of this paper. Bailey reports a case of hæmorrhage into the gland resulting in a serious destruction of its substance; Mitchel records a case in which an aneurism completely eroded the body; Burr and Reissman found a tumor which entirely destroyed the pituitary body; Hinsdale found a round-cell sarcoma occupying the sella turcica, and states that Boyce found the hypophysis wholly absent in a case of phthisis. Though in all of these instances complete or nearly complete destruction of the gland had taken place, no acromegalia was present. I have already called attention to those essential points which are always found in a tumor of the hypophysis cerebri associated with, or causative of, the disease. It is difficult to understand how, in the face of such overwhelming evidence, the hypophyseal destruction theory can be supported.

Unfortunately, nothing new, which seems to promise any considerable success, has been advanced in the way of treatment. Napier has stated, in a brief society report, that he has secured beneficial results in one case by the administration of ovarian, thyroid and pituitary extracts. Garland agrees with the great majority of practitioners that no good result follows the use of hypophyseal extracts. All, with few exceptions, advise symptomatic and hygienic treatment alone, and of such measures enough have already been indicated in the body of the paper.

PATHOLOGICAL INSTITUTE OF THE NEW YORK
STATE HOSPITALS, DECEMBER 18, 1898.

DESCRIPTION OF PLATES.

Plate I.

Figure 1.—Photograph of a well developed case of acromegalia at present under the treatment of Dr. Joseph Collins, to whom the author is indebted for the opportunity of this reproduction. The inclination of the head downward and to the left is characteristic of paresis of the right superior oblique muscle.

Figure 2.—Photograph of Case II, taken three years previous to death, and before symptoms of acromegalia were noticed.

The features present several characteristics which are indicative of incipient acromegalia. Note the globular end of the nose, the heavy orbital arches and the prominent malar eminences. The inferior maxilla, though somewhat large and heavy, does not yet show the prognathism usually present in the disease. The thick lips and the heavy lobe of the left ear are perhaps early evidences of the process. The peculiar hair of the patient is well shown in the photograph. The short neck and the prominent shoulders are noticeable in this photograph, but are much more marked in fully developed cases, as shown in the other photograph. (Fig. 1).

Plate II.

Figure 1.—Skiagraph of the hand of a male, æt. 38 years, presenting advanced and typical manifestations of acromegalia. Reduced. The deformities shown in this reproduction are very characteristic. It should be noted that while the bones of the fingers are apparently of normal length, the fingers, because of the outlines of the soft tissue, appear to be short in proportion to the enormously large palm.

The osteophytic overgrowth of the ungual phalanges is very marked in this case; the distal margin is most affected, although the circumference of the articulating surfaces also shows considerable exostosis.

It will be noticed that all the seats of muscular or fascial attachment on the phalanges and metacarpal bones are exaggerated. This is also true, though in less degree, of the bones of the carpus. The sesamoid bone of the thumb is apparently slightly enlarged.

Figure 2.—Skiagraph of the normal hand of a large male. Reduced equally with Figure 1.

Presented for comparison of the changes in the preceding figure.

Plate III.

A drawing from a section of kidney of Case No. I, the specimen was hardened in formalin (Schering), imbedded in paraffin, and stained in hæmatoxylin and eosin. Leitz objective, No. 7.

A. Cross section of convoluted tubule.
B. Collecting tubule.
C. Glomerulus.
D. Vein filled with blood cells.

The interstitial tissue increase is quite apparent, especially in the region of the capillary tuft. Connective tissue cells are numerous and distinct throughout the entire stroma. The renal cells in this portion of the section are normal. The irregularly distributed pigment deposit associated with bronze diabetes in this case is very striking, especially in the bases of the cells. The pigment granules in the cells of the functional portions of the collecting tubules are very much larger than in the secretory tubules. A considerable amount of the pigment lies free in the newly formed stroma.

Plate IV.

Figure 1.—Liver, Case I.—The specimen was hardened in formalin, imbedded in paraffin, and stained with Van Gieson's picro-acid fuchsin. Sketched under Leitz objective No. 7.

The drawing shows moderate increase both of the basement substance and the connective tissue cells in the interlobular spaces, as well as degeneration and fatty infiltration of the hepatic cells. The pigment deposit associated with the bronze diabetes mentioned in the text (p. 503), is not well shown by this method of staining.

Figure 2.—Pancreas, Case I.—Specimen hardened in formalin and imbedded in paraffin. The section was stained with iron hæmatoxylin. Sketched under Leitz objective No. 7.

The drawing shows interstitial increase with atrophy of the glandular acini.

Figure 3.—Section which shows karyokinesis of the endothelial cells of a capillary in the heart of Case II. Specimen hardened in formalin imbedded in paraffin, and stained with iron hæmatoxylin.

Sketched under Leitz $\frac{1}{12}$ oil immersion, ocular No. 4, reduced one-fourth.

A. Endothelial cells of a capillary showing karyokinetic figures.

B. Endothelial cells of a capillary in cross section which show greatly enlarged nuclei.

Figure 4.—Section of the thyroid gland of Case I, hardened in formalin, imbedded in paraffin and stained with Van Gieson's picro-acid fuchsin.

Figure 5.—Section of the persistent thymus body from Case I, hardened in Müller's fluid, imbedded in paraffin and stained with hæmatoxylin. Sketched under Zeiss objective D. D., ocular No. 4, reduced one-third.

The plate shows the normal structure of a persistent thymus gland in early youth.

Figure 6.—Voluntary muscle fibres from the tongue of Case II. Hardened in formalin, imbedded in paraffin and stained with hæmatoxylin and picric acid. Camera lucida, Zeiss objective D. D., ocular No. 4, reduced two-thirds.

The fibres show proliferation of the muscle nuclei. Although not shown in the drawing several of the nuclei in the same field presented pictures of mitosis. The fibres sketched were purposely chosen to show the changes to a lesser degree than elsewhere in the section.

Figure 7.—Section of heart muscle from Case II. Hardened in formalin, imbedded in paraffin, and stained with hæmatoxylin and eosin. Camera lucida, Zeiss objective $\frac{1}{12}$, ocular No. 4, reduced two-thirds.

The figure shows the atrophied muscle cells with their large and irregularly shaped nuclei. The hyperplastic connective tissue stroma is shown in Figure 3.

Plate V.

Figure 1.—Portion of the base of the skull from Case I, showing the enlarged sella turcica and the elongated and thinned posterior clinoid plate. Reproduction actual size.

A. Enlarged pituitary fossa.
B. Perforation in the elongated posterior clinoid plate.
C. Atrophied optic nerves.
D. Sixth cranial nerve.

Figure 2.—Sagittal cross section through the centre of the enlarged hypophysis of Case II. Specimen hardened in formalin, imbedded in celloidin, and stained with Van Gieson's picro-acid fuchsin. Camera lucida. Details under Zeiss objective A. A.

A. Posterior or neural lobe.
B. Anterior or glandular lobe.
C. Adenoma.
D. Acini containing colloid substance.
E. Connective tissue capsule.
F. Infundibulum.

The adenomatous character of the tumor is apparent, even with the low magnification represented in the sketch. It will be noticed that the anterior lobe contains much more connective-tissue stroma than the tumor, otherwise under this power their structure appears quite similar. A large number of blood vessels can be seen in every part of the section. (See p. 519).

Plate VI.

Figure 1.—Section of the hypertrophied prehypophysis from Case I. Specimen hardened in Lang's solution and imbedded in paraffin. Section stained in hæmatoxylin and eosin. Zeiss objective $\frac{1}{12}$, ocular No. 4, full size reproduction.

A. Chief cells, the protoplasm of which has reacted to the stain in only a slight degree.
B. Chromophilic cells.

The section clearly shows the glandular structure of the normal hypophysis and consequently the hyperplastic nature of the enlargement, indeed the section could not be differentiated from one of a normal prehypophysis, were it not that there is a somewhat smaller amount of stroma present. The difference in shape and size between the chief and chromophilic cells is quite evident, and the variation in the staining reaction is indicated by the darker shading of the chromophilic cells. (See p. 500).

Figure 2.—Adenoma of the hypophysis in Case II. Specimen hardened in alcohol and imbedded in paraffin. Section stained with hæmatoxylin and eosin. Camera lucida, Zeiss objective $\frac{1}{12}$, ocular No. 4, full size reproduction.

A. Thin-walled blood vessel, filled with blood corpuscles.
B. Connective tissue stroma enclosing a small vessel.

The uniformity of all the cells which make up the growth and their close resemblance to the chromophilic cells of the normal prehypophysis would seem to indicate that the adenoma originated from the chromophilic cells alone. The granular cytoplasm is well shown in the drawing, as is also the active response of these granules to the eosin.

Figure 3.—Isolated cells from the hypophyseal adenoma in Case II. Specimen hardened in alcohol and imbedded in paraffin. Section stained with Merkel's indigo-carmine. Zeiss objective $\frac{1}{12}$, ocular No. 4; tube length 160 mm., full size reproduction.

The granular cytoplasm of these cells has responded to the indigo, a reaction which takes place with the chromophilic cells of the normal prehypophysis, the chief cells in the normal tissue, meanwhile taking the carmine stain, as do the nuclei in both varieties of cells.

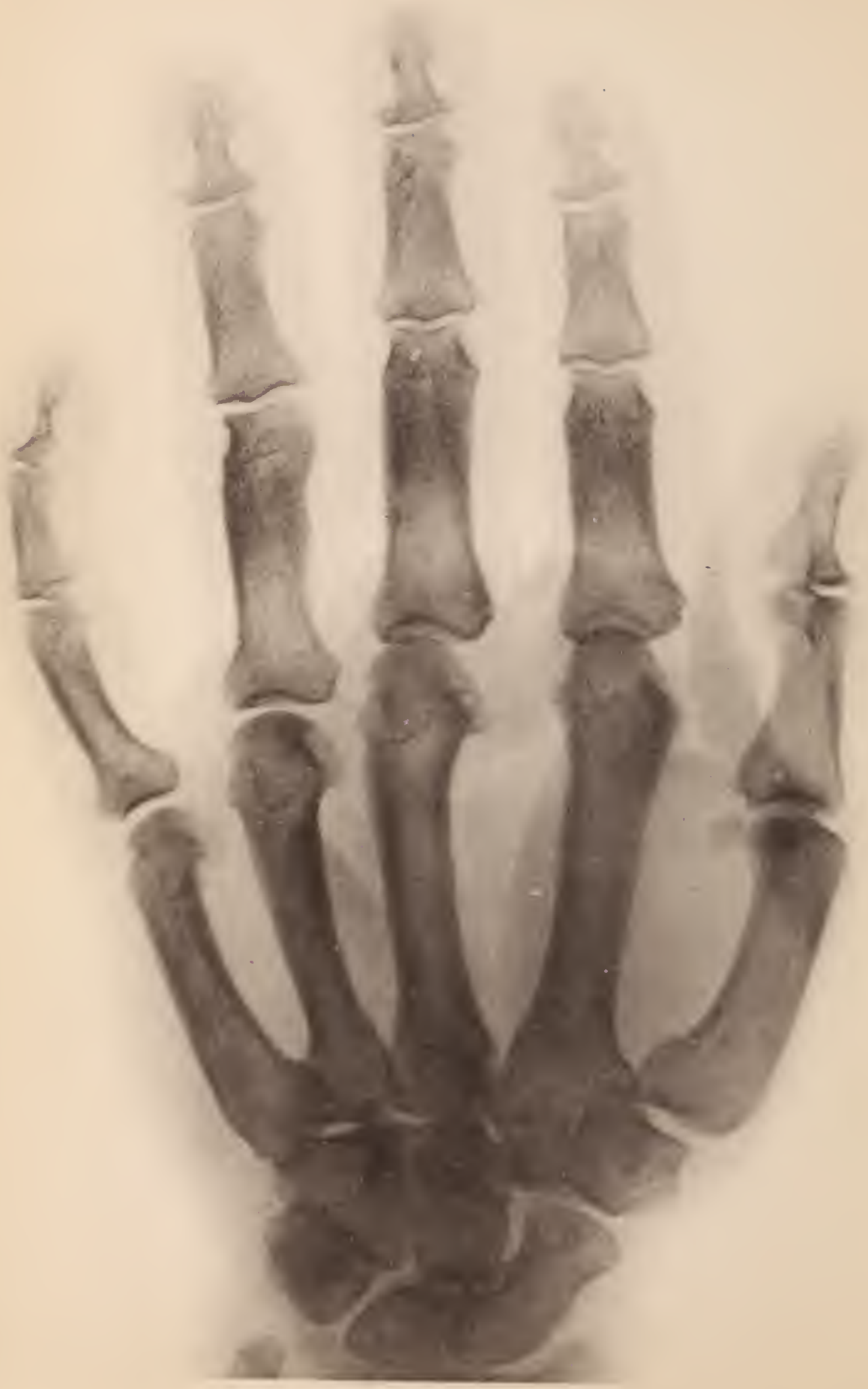
Figure 4.—Section of a sympathetic ganglion of the solar plexus, Case I. Specimen was hardened in formalin (Schering) and imbedded in paraffin. The section was stained with eosin and Nissl methylene blue. Zeiss objective $\frac{1}{12}$, ocular No. 4; full size reproduction.

A. Normal ganglion cells.
B. Completely degenerated ganglion cells.
C. Cells showing a less extreme degeneration.

(See text, p. 593, concerning the nature of this degeneration).

FIG. 1.

FIG. 2.



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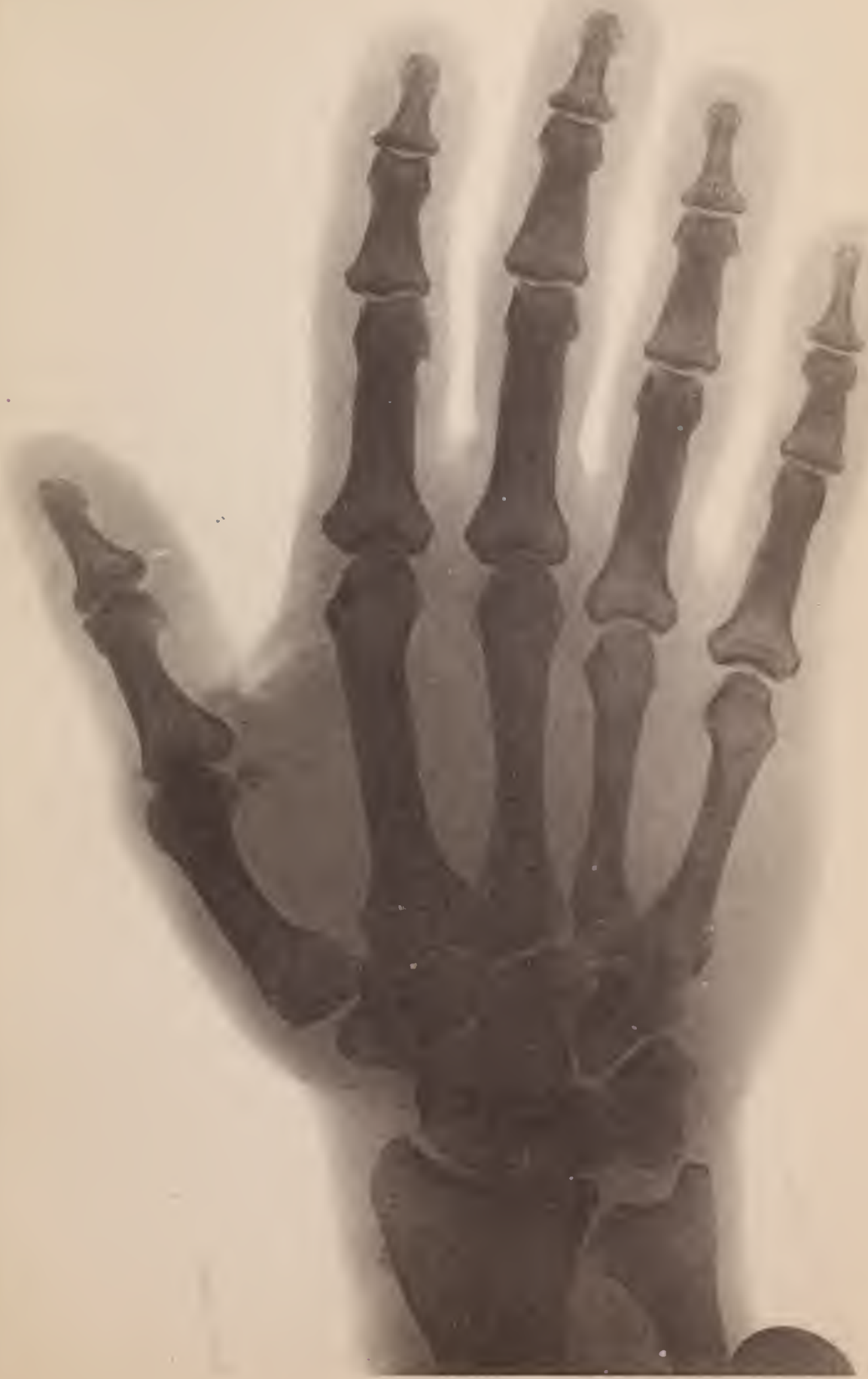

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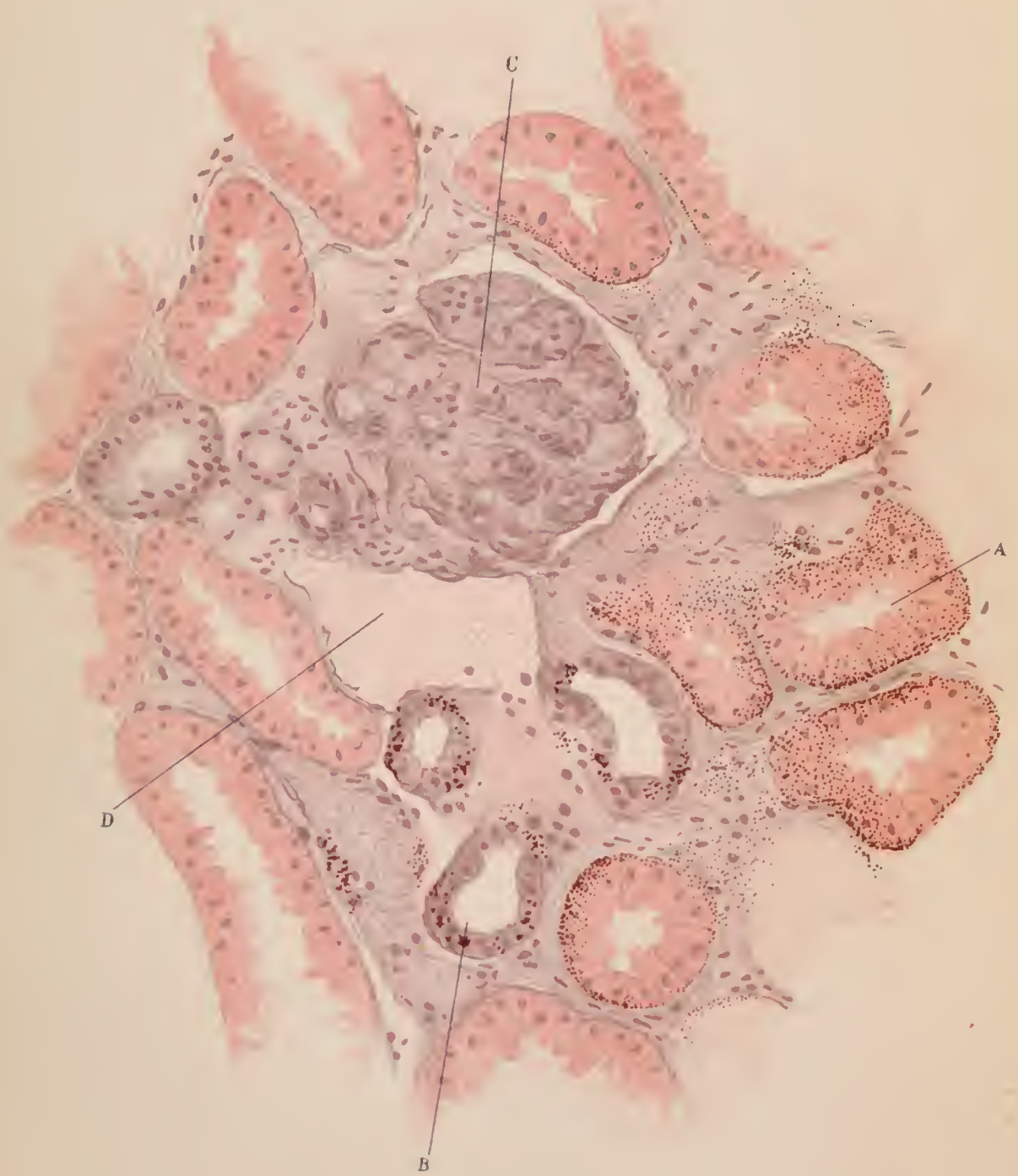
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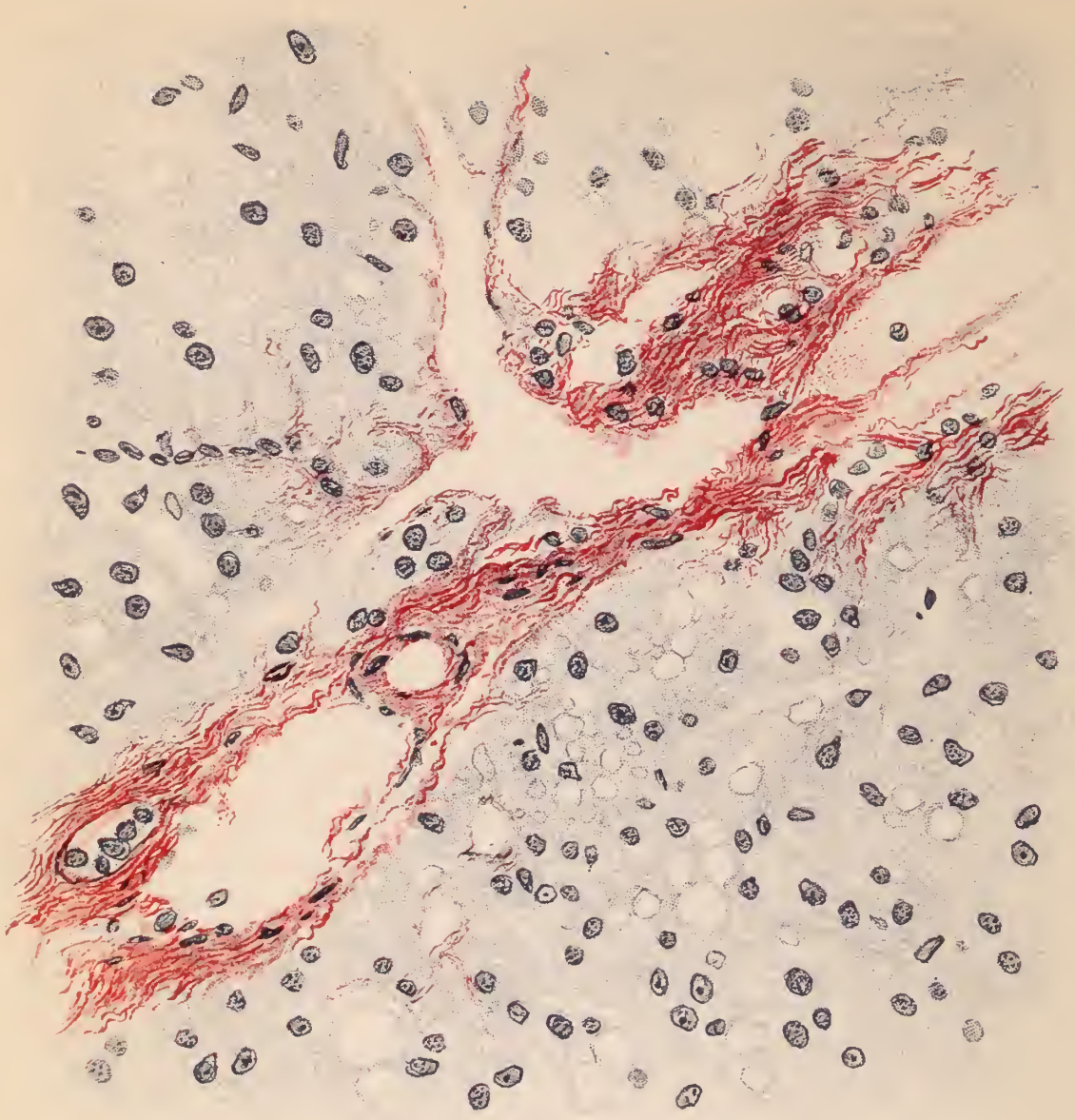

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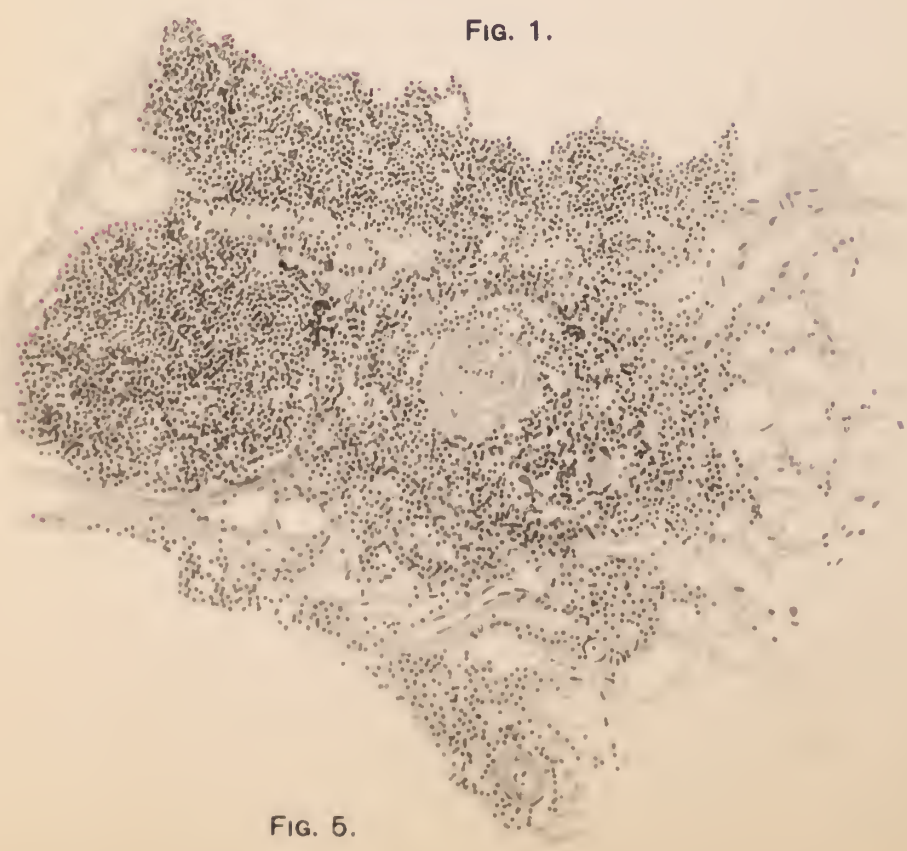

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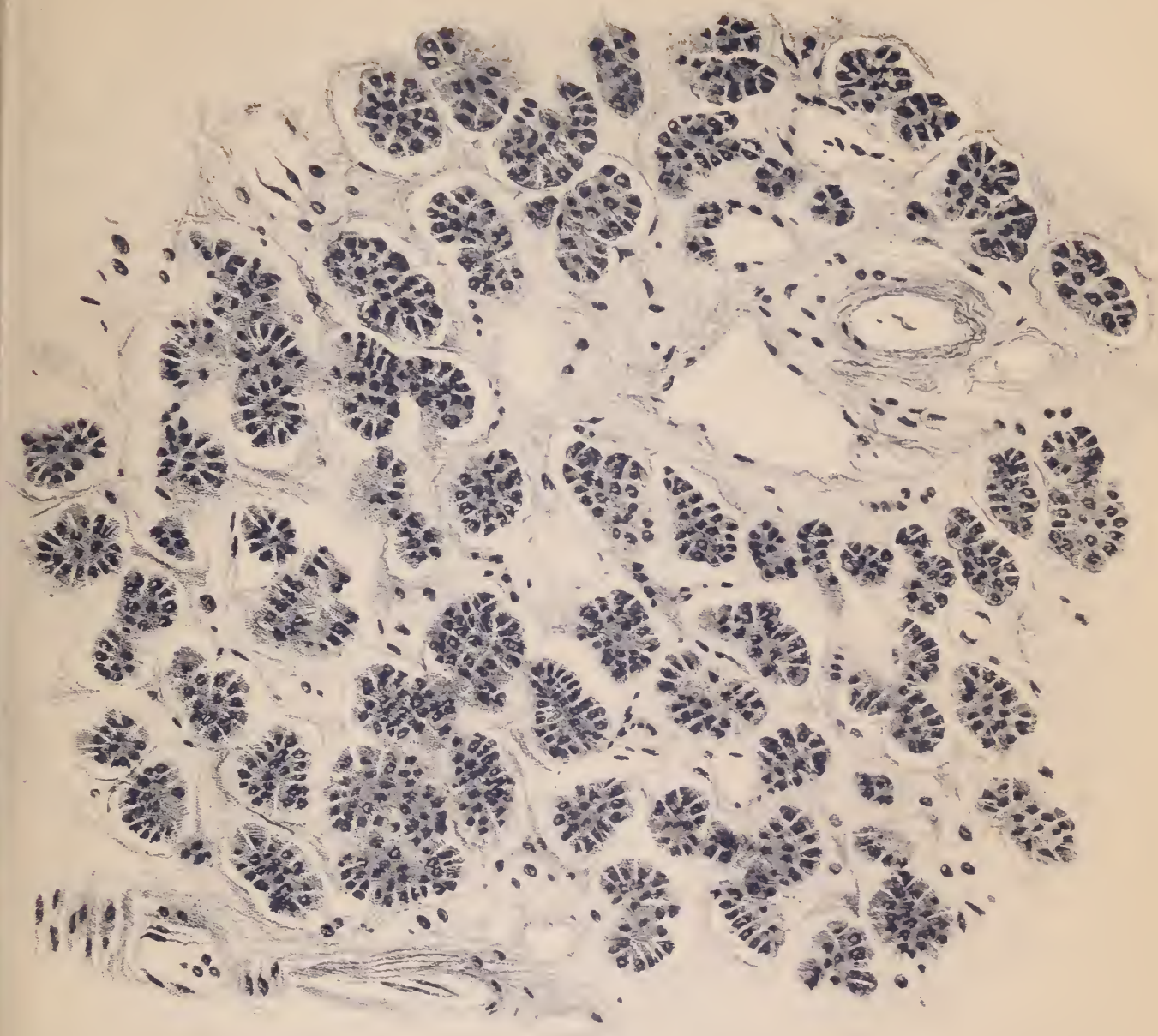

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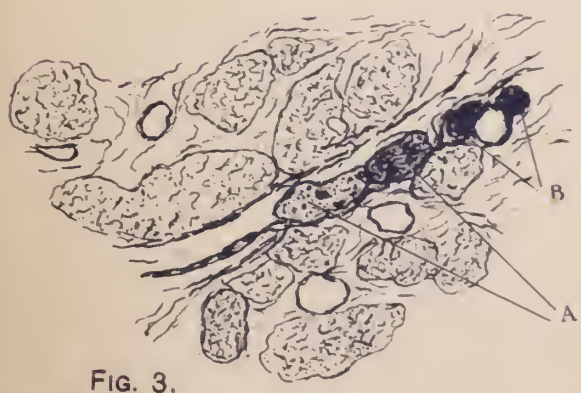

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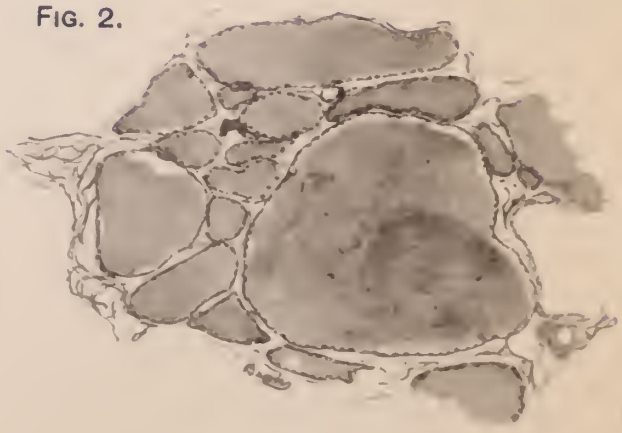

FIG. 4.

FIG. 7.

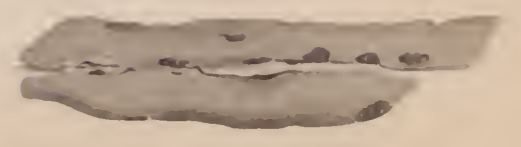

FIG. 6.

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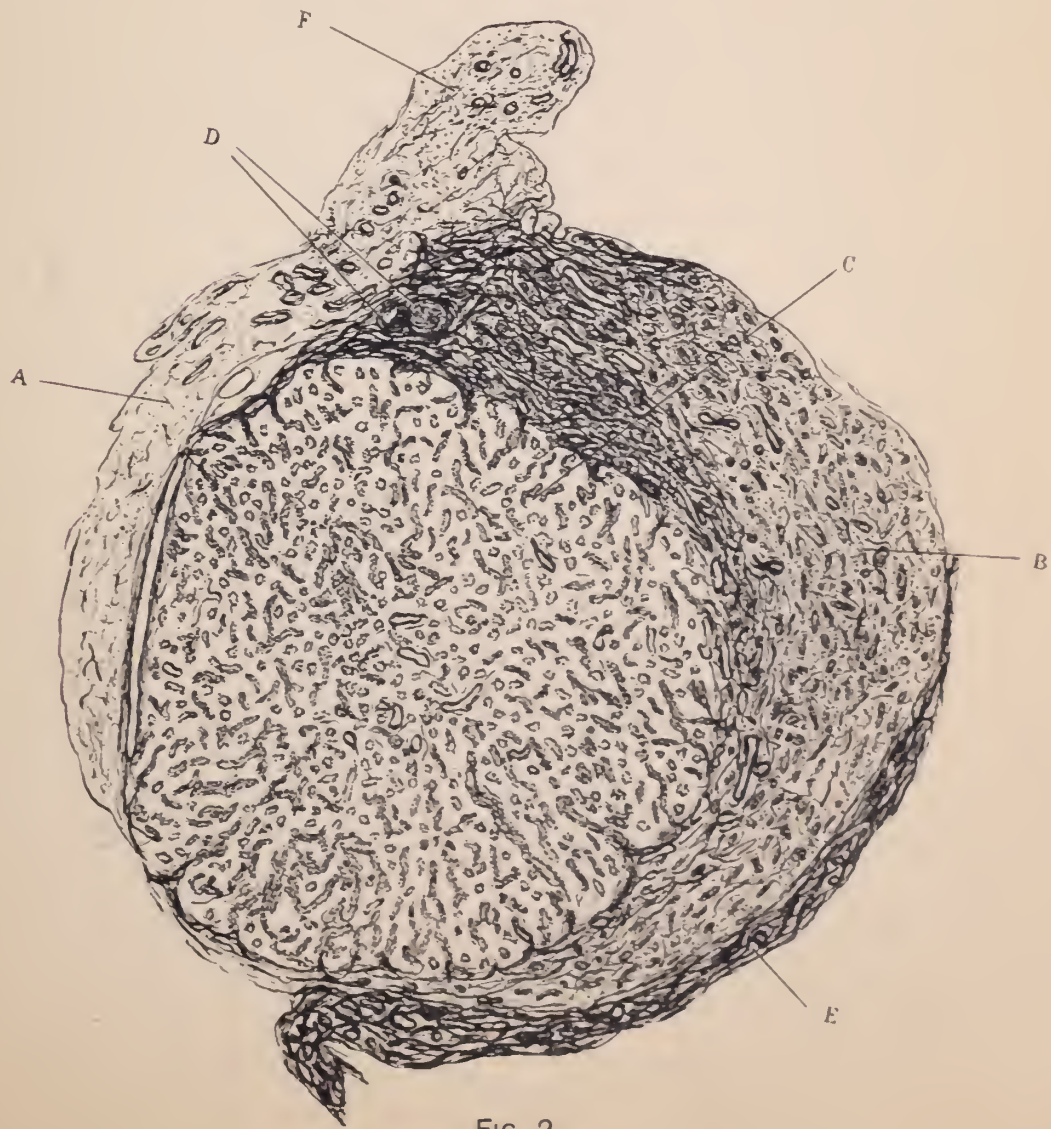

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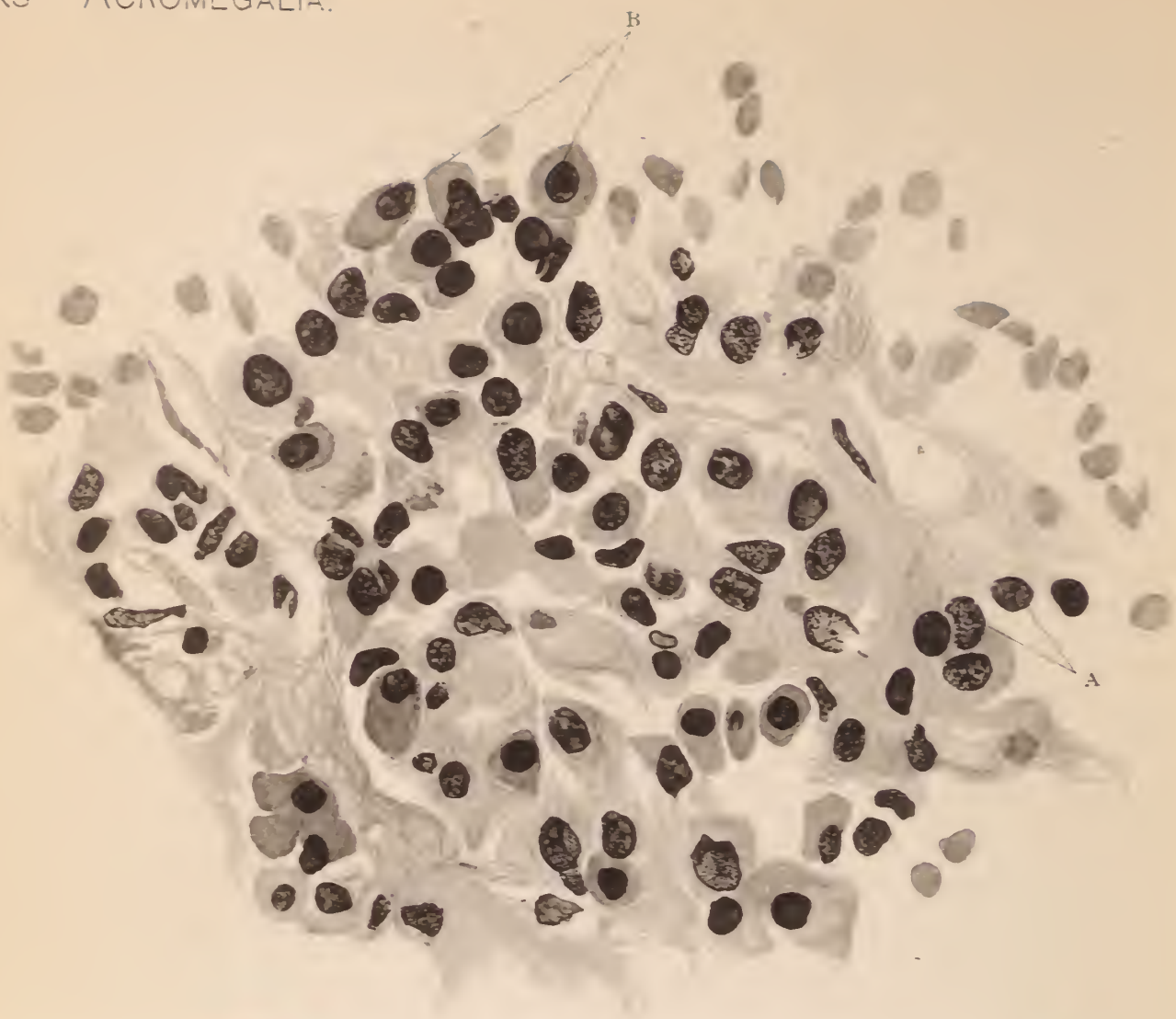

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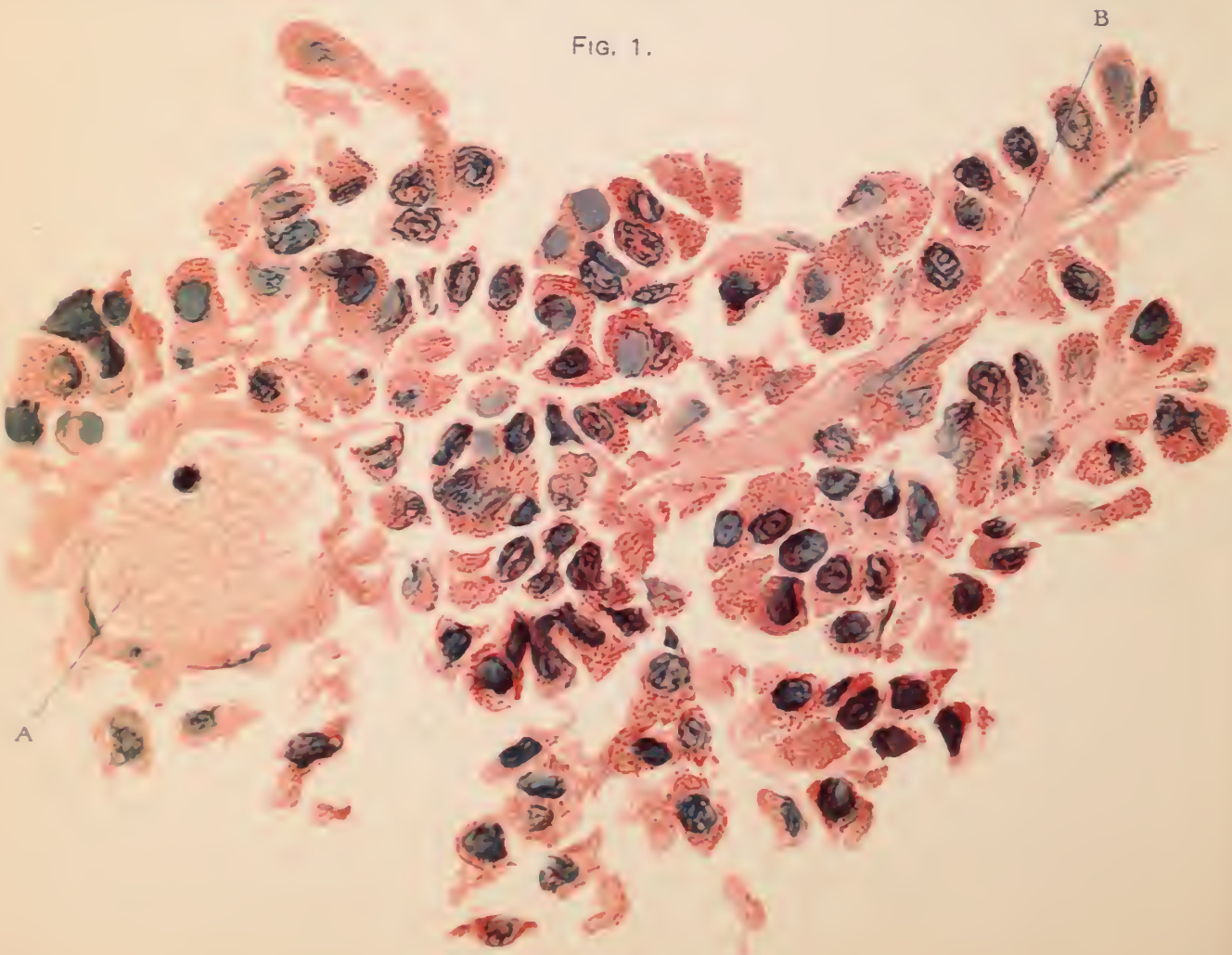

FIG. 2.

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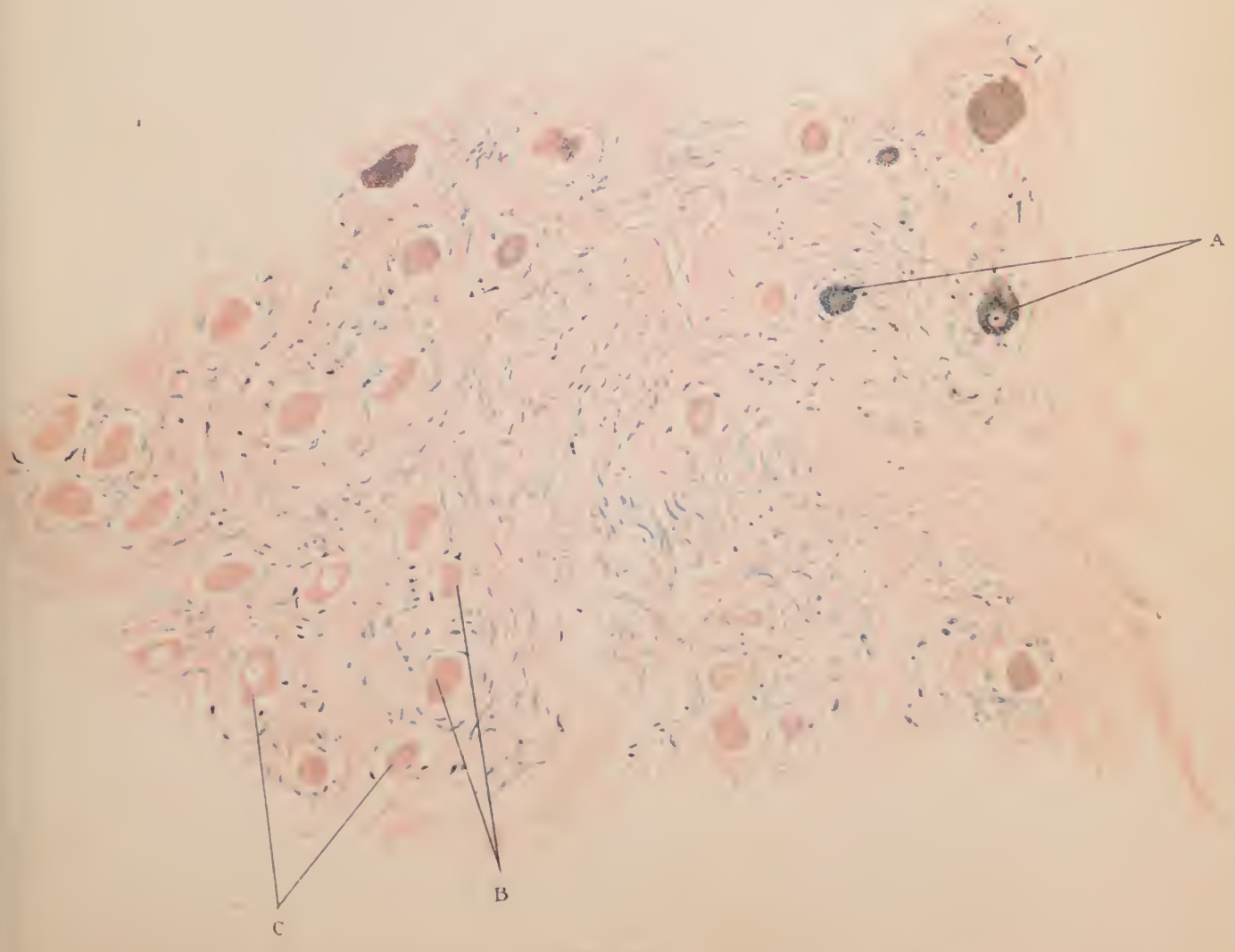

FIG. 4.

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I am indebted to Mr. E. A. Tibbetts of the Library of the Surgeon General's Office (U. S. Army) for the verification of several references to articles in foreign publications not accessible in New York.—A. B.

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DIMENSIONS OF THE NORMAL PITUITARY FOSSA OR SELLA TURCICA IN THE WHITE AND THE NEGRO RACES.—AN ANATOMICAL STUDY OF FIFTY-SEVEN NORMAL SKULLS OF WHITE AND SIXTEEN NORMAL SKULLS OF COLORED INDIVIDUALS.

WITH THREE PLATES.

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Since it has been repeatedly demonstrated that marked enlargements of the pituitary body are of a pathognomonic nature, it becomes desirable to learn the normal dimensions of the hypophysis, and also its normal range of variations in size.

The pituitary gland itself is not well adapted for accurate measurements.* The organ is small, very yielding, and does not present any positive landmarks for measuring. Furthermore, the gland is frequently injured in extraction. Under these circumstances we find an equally good if not much better subject for hypophyseal measurements in the enveloping bony fossa.

We have thought that measurements of the fossa might be of value in identifying and differentiating the skeletons of acromegalia and gigantism, osteo-arthropathie hypertrophiante, etc., and also be of some anthropologic value in the differentiation of races. We must, however,

* Zander records the variations in the diameters of the normal hypophysis as follows: Sagittal diameter, 6.0–10.5 mm.; frontal, 10.0–14.5 mm.; vertical, 5.0–9.75 mm. According to Schonemann, Boyce and Beadles the average weight is 0.6 gr.

remember that the measurements of the fossa can never be an infallible index of the condition of the hypophysis. This may be comparatively little changed in size and still be the seat of hyperplasia which Brooks, in the preceding paper, shows to be the specific and definite causal process in acromegalia. It should not be expected that the early phases of hyperplasia can be detected by measurements either of the pituitary body or fossa. Microscopical examination of the hypophysis with especial reference to cytologic structural details affords the only means of determining these early cellular changes accompanied by very slight enlargements of the hypophysis. These minor degrees of hyperplastic enlargement, although sufficient to initiate the train of acromegalic phenomena, might fall within the normal range of variations of the size of the hypophysis. On the other hand, enlargement of the pituitary fossa in the skeleton does not in every case indicate acromegalia, for Brooks shows that neoplasms of the hypophysis, although they may produce an enlargement of the fossa, have no causal relation to acromegalia. Thus we may expect to find enlargement of the pituitary fossa in non-acromegalic skeletons; and the earlier changes in acromegalic skeletons with but little if any enlargement of the fossa beyond the maximum of the normal range of variations. The latter condition, however, would be of rare and exceptional occurrence. In the great majority of cases the acromegalic skeleton must show various degrees of unmistakable enlargement of the pituitary cavity due to the gradual absorption of bone about the hyperplastic or adenomatous gland. Since enlargements of the hypophysis, not associated with acromegalia, are of very rare occurrence, an enlarged pituitary fossa, especially when associated with noticeable changes

in other parts of the skeleton, would convey at least a strong suspicion of acromegalia.

The pituitary fossa, or sella turcica, is not really a perfect mould of the hypophysis, but the excess is small and also constant in a series of measurements. In addition to the hypophysis the cavity generally contains some alveolar tissue. This is especially true of the anterior part of the sella and of its opening. The connective tissue, however, is never present in such amount as to materially influence the dimensions of the fossa which correspond very closely to the volume of the pituitary body. When the hypophysis enlarges, the sella enlarges correspondingly, both in size and direction. An independent enlargement of the sella or an independent increase of the connective tissue about the gland, has never been reported. Thus if we know both the average dimensions of the pituitary fossa and their possible variations in a normal state, any excess in the dimensions of the structure can be taken as a positive indication of an enlargement of the hypophysis through neoplasm or hyperplasia. Knowing the normal measurements and their variations, we would also be enabled to judge as to the degree of enlargement of the organ. Both these possibilities, especially when taken in conjunction with abnormal features in other parts of the skeleton, may occasionally prove of great value in determining a differential diagnosis.

Having access, through the courtesy of Prof. Huntington, to the Anatomical Department of the School of Medicine of Columbia University, where are large numbers of normal skulls, I undertook the task of ascertaining the average size and the limits of variations of the normal sella turcica.

The study was made separately on skulls of white males

and females; I measured also a number of skulls of male and female negroes, and the data will be included for comparison. Only normal and adult specimens have been included; I have not been able to obtain a sufficient number of skulls of children and adolescents, and am unable to give satisfactory data of the variations of the pituitary fossa during the growth period.

The first point in this investigation was to establish fixed landmarks, from which all subsequent measurements on different skulls could be taken. This proved to be quite difficult as the contours of the fossa are not well defined; the walls of both sides as well as the top being incomplete. The shape of the fossa differs from almost spheroidal, to obliquely or horizontally ellipsoidal; its walls and the immediate neighboring parts are subject to much variation in different skulls.

The more or less rounded shape of the sella renders it fit for three measurements, namely, maximum length, width, and depth. To clearly indicate the landmarks for these three measurements,—landmarks which I decided upon only after numerous trials,—it will be necessary to review with some detail the anatomy of the fossa and adjacent bony structures.

Proceeding from the posterior angles of the cribriform plate of the ethmoid, backward along the flat surface of the body of the sphenoid, the first distinct structure met with is a low, but in a large majority of cases, well defined transverse ridge. (Fig. 1, *a*).* This bony elevation marks the anterior boundary of a slightly depressed space, which contains anteriorly a slight furrow, the optic groove, and behind this an elevation, the olivary eminence. The extremities of the ridge surmount the optic foramina and

* The indices in this description refer to Figs. 1 and 2 of Plate I.

blend with the bases of the anterior clinoid processes. This ridge, which may advantageously be termed the *anterior olivary ridge*, is from 2.0 cm. to 3.0 cm. long, and usually about 1.2 cm. posterior to the posterior angles of the cribriform plate.

The space which contains the optic groove and the olivary eminence is, as will be seen later, of a certain importance and deserves a close description.

The optic groove is seldom perfect and frequently is very shallow or indistinct. The surface of the olivary eminence is more or less convex, both laterally and antero-posteriorly. The antero-posterior convexity varies considerably, in some cases the surface is almost flat, while in others the posterior part of the surface slopes down very abruptly. Laterally the olivary eminence is bounded by the carotid *semi-foramina*. Posteriorly, the boundary of the eminence is formed by another distinct and almost constant bony elevation, which terminates on each side in a short, sharp point, termed the second or middle clinoid process. This second, or *posterior olivary ridge*, forms the anterior border of the pituitary fossa, and its centre (Fig. 1, *b*), is our first landmark, namely, the anterior point from which we take the antero-posterior diameter, or the length, of the sella turcica.

The space between the anterior and posterior olivary ridges is bounded laterally by the mesial surfaces of the anterior clinoid processes. If well formed, these processes proceed from the extremities of the anterior olivary ridge, in front and outside of the optic foramina. Their mesial lines converge (in a few skulls they diverge) a little in their distal half. Their external lines, which are continuous with the posterior borders of the lesser wings of the sphenoid, converge gradually throughout

their whole length. These two lines, *i. e.*, the inner and outer borders of the anterior clinoid process, meet in a sharp or blunt point, marking the free extremity of the process. These extremities are usually about opposite the middle of the sella turcica; in some skulls they terminate somewhat more anteriorly. They can be utilized, as will be seen later, for landmarks of a certain measurement.

Progressing still backward from the posterior olivary ridge, we meet the sella turcica itself, which presents for examination an anterior and posterior wall, and a base; the sides and roof are deficient.

Holding the skull in its standard position, (*i. e.*, horizontal or alveolo-condylian line of Broca), we see that the anterior wall of the pituitary fossa is not vertical, but slopes somewhat downwards and backwards. From side to side it is flattened, or slightly concave, especially at the base. The borders of this anterior wall are very blunt and convex, sloping away gradually into the carotid depressions on their exterior.

The base of the pituitary fossa is generally somewhat narrower than the anterior wall, although the gradual outward slope may give the appearance of greater breadth. The direction of the base may be almost horizontal, but, most frequently, and especially in the female, it is inclined in varying degrees downward and backward. The sides slope to the considerably lower level of the carotid grooves.

The surface of the base shows an oblong, more or less shallow but distinct depression, which lodges the lower part of the hypophysis. The borders of this depression are usually well marked, and as directly beyond them the parietes begin to slope downward, they offer us the only possible landmarks from which to measure the width

of the pituitary fossa. For this measurement we choose the highest points on these borders, where they are most widely separated (Fig. 1, *e e*). Occasionally, unusual breadth and indefiniteness of these borders may make selection of the proper points somewhat difficult, but such instances are exceptional, and with some care the proper measure can generally be determined. The width thus obtained will be but little less than the maximum width of the hypophysis but sufficiently accurate for all practical purposes.

Posteriorly, the pituitary fossa is surmounted by a high, flat process of bone, the dorsum sellæ. This bony lamella rises from above the spheno-occipital suture, and in the adult skull is directly continuous with the basilar process of the occipital bone. It is inclined somewhat forward, and in some cases is narrower at the base than at the top. The top of the lamella is free, and the margins irregular and thickened. The superior border presents a more or less marked notch in the middle, and terminates on each side in a small conical body, the third or posterior clinoid process. Posteriorly, the dorsum sellæ is rough and flat, while the lower part is slightly concave. This concavity is continuous with that of the basilar process, together forming a distinct, broad groove. Anteriorly (ventrally) the dorsum is in most cases but slightly concave; however, in a certain percentage of cases it shows a pronounced rounded depression.

For our purpose of measuring the sella turcica, the most interesting part of the dorsum sellæ is the middle of the anterior edge of its upper border (Fig. 1, *c*). This point is the only suitable posterior landmark for the measurement of the antero-posterior diameter of the fossa, the anterior landmark being, as already stated, the middle of the posterior olivary ridge (Fig. 1, *b*).

The notch in the centre of the upper border of the dorsum sellæ, as well as the occasional marked depression on its ventral surface, are indications of an original deficiency in the lamella and we find such a deficiency in varying degrees in lower animals. Occasionally (in man), the notch is unusually deep, and in such a case our posterior landmark for the length measure of the fossa must be shifted a little on the anterior edge of the dorsum to one or the other side of the notch. Such a shifting of one landmark of the measure will not cause any appreciable change in the value of this measurement. The thickness of the upper border of the dorsum sellæ should never be included in this measurement; it is very uneven in different skulls.

The lateral and the antero-posterior diameters obtained, it remains for us to measure the depth of the fossa. The best method, I find, for taking this measure is as follows, lay a thin, narrow piece of steel or wood over the fossa from before backwards: its anterior end should rest on the top of the olivary eminence, and its posterior part should lie over the notch in the superior border of the dorsum sellæ (Fig. 2, *c*). From the under surface of this improvised roof, when in the proper position, we secure a perpendicular to the deepest depression in the base of the pituitary fossa; the length of this line is the measurement of the depth of the fossa (Fig. 2, *x* to *f*). This perpendicular measure is best obtained by a small, graduated steel rod; with a little more care it may be accurately determined by a delicate compass.

The most simple and practical way to make this measure is to use a piece of an old steel tape measure for the horizontal lamella or roof, and a tooth-pick for the vertical rod, pressing the latter, when in the proper position, a

little against the sharp edge of the former, and then measuring on the tooth-pick the height of the indentation.

The depth thus obtained is generally a little too great, but the excess is seldom more than 1 mm. and is unavoidable. This variation is not corrected in our calculations. Theoretically, the proper anterior landmark in measuring the depth of the sella would be the posterior olivary ridge. (Fig. 2, *b*). This ridge, however, though fully satisfactory for the length measurement, is in different skulls situated at such varying planes of height, that it can not be assumed to represent in every case the real height of the hypophysis and can not be well utilized for the depth measure. The point of the olivary eminence, though a little too high, is a much more stable landmark. Furthermore, the measurement from this point is very much easier to take than from the posterior olivary ridge.

The three principal measurements of the pituitary fossa obtained, we may consider two secondary ones. When we look at the region of the fossa from above, we notice that the anterior olivary ridge, the inner surface of the first or anterior clinoids, and the anterior line of the superior border of the dorsum sellæ, form an interrupted bony ring, situated somewhat above (superior to) the fossa itself. In some skulls this ring is completed through the union of the first and the third clinoid processes. This ring is capable of two measurements, the length and the width. The width of the ring is the distance between the points of the anterior clinoids. The antero-posterior diameter of the ring can be obtained from the centre of the anterior olivary ridge to the centre of the superior border of the dorsum sellæ. (Fig. 2, *a* to *c*). These measurements, however, are of little medical or anatomical importance.

Having discussed in detail the conformation and the manner of obtaining the measures of the pituitary fossa, I can now give the results of the measurements.

In the manner described above the sellæ were measured in four series of skulls of various white races and in two other series of American negroes. The number of specimens in the first two series I consider sufficient for the establishment of a correct average of measurements, and the scales of normal variations are undoubtedly almost complete. The number of the negro skulls is somewhat small; nevertheless they are sufficient to indicate in a gross way the essential similarities and differences of measurement in the pituitary fossæ of the white and black families. I should expect these differences to be more marked in pure African negroes, in whom all chances of admixture of white blood could be excluded.

I did not stop at the crude principal measurements of the fossa, but have endeavored to establish certain comparisons, in order to control the simple measurements.

It would seem reasonable to assume that the volume of the pituitary fossa would bear some relation to the capacity of the skull. The volume or capacity of the skull increases in certain proportion with the size and particularly with the height of the body, and the pituitary fossa, being a part of the cavity of the skull, might be expected to enlarge correspondingly.

Thus we would expect to find a perceptibly larger pituitary fossa in the male skulls as compared with female skulls and a smaller fossa in smaller people of either sex.

But it is quite difficult to obtain the correct cubical volume of the pituitary fossa, and in most of the cases I examined, a previous opening of the skull made a measure

of the capacity of the skull impossible. It was necessary, then, to look for the most satisfactory substitute for capacity.

Of head measurements no single one furnishes a reliable index of the size of the cranium. The most satisfactory substitute for skull capacity is expressed by the maximum circumference of the cranial vault, and we have utilized this measure in place of that of cranial capacity.

In the place of the capacity of the pituitary fossa, we can utilize any of its three principal diameters. I found it far more satisfactory, however, to secure an average of the length, width and depth of the fossa, and compare this average with the circumference of the skull. This average constitutes a module, which is a purely mathematical, but none the less practical, substitute for the real capacity measure of the fossa, and corresponds to the skull module of Schmidt,* *i. e.*,

$$\frac{Length + Width + Height\ of\ Skull,\ Max.}{3}$$

By comparing the module of the pituitary fossa with the maximum circumference of the same skull, we obtain a number which clearly expresses the size relation of the two measures, and this is sufficient for our purpose.

To obtain this number, we first state the module of the pituitary fossa, according to the formula of Schmidt:

$$\frac{Length + Width + Depth}{3}$$

Multiply this by 1000 and divide the result by the circumference of skull expressed in centimetres. The module of the fossa is thus expressed in thousandths of the circumference measurement of the skull.

* This formula has proven very valuable to the anthropologist.

We might choose the percentage instead of the per thousand, but the resulting number would be very small and inconvenient.

I think that the measurements of the pituitary fossæ of the four series of skulls mentioned should be given in detail. If so stated, the reader who may wish to give a closer attention to the subject will find himself supplied with ample data. These detail measures, however, can well be placed in an appendix, not to disturb the continuity of the paper. In this place I will state only the averages and the variations of the measures for each group.

THE LENGTH, OR ANTERO-POSTERIOR DIAMETER OF THE PITUITARY FOSSA. (See Plate II, Fig. 1).

	White Male.	White Female.	Negro Male.	Negro Female.
Averages:	1.11 cm.	1.00 cm.	1.09 cm.	1.06 cm.
Variations:	0.75–1.45 cm.	0.75–1.30 cm.	0.85–1.25 cm.	0.80–1.40 cm.

In the cases of the white male and white female, where the number of skulls examined is large, the variations can be expressed to advantage graphically by columns or curves. (See Plate II, Fig. 1):

The wide variation of the length measure is striking. The same thing will be observed more or less with the other measures of the pituitary fossa. The maximum of variation reaches with some of the measures fully 100 per cent. Nevertheless, the majority of measurements of each series, group themselves around the average and the extremes must be considered as exceptions.

The average length of the fossa does not differ greatly in the four series. There is a decided difference in the dimensions of the white male and white female, the latter averaging about 1 mm. shorter. There is a similar but much smaller difference between the sexes in the negro.

The scale of variations appears to be much smaller in the negro male than in the white male.*

No very appreciable or stable differences in the measurements could be found corresponding to brachy- or dolichocephaly. The average length of the fossa, however, is less in the very short than in the very long skulls. This condition is corroborated by the two maxima around the averages shown in the columns which represent the length variations. (Plate II, Fig. 1). The other two measures of the fossa, namely, width and depth, do not show appreciable and stable differences relative to the shape of the skull.

The Width, or Lateral Diameter of the Pituitary Fossa.
(See Plate II, Fig. 2).

	White Male.	White Female.	Negro Male.	Negro Female.
Averages:	1.15 cm.	1.08 cm.	1.05 cm.	1.21 cm.
Variations:	0.70–1.50 cm.	0.80–1.50 cm.	0.95–1.40 cm.	1.00–1.55 cm.

The differences in the four series are somewhat more pronounced in the width measurements than in the length. The average fossa in the white female is again appreciably smaller than that of the white male. Curiously, this difference in the black is reversed; the breadth of the female fossa averaging 1.6 mm. greater than the male. This difference cannot be satisfactorily explained. Comparisons of the fossæ of the black and the white male show a lesser width as well as length in the latter. The scales of variation are again decidedly smaller in the black.

Depth of the Pituitary Fossa.
(See Plate II, Fig. 3).

	White Male.	White Female.	Negro Male.	Negro Female.
Averages:	0.91 cm.	0.94 cm.	0.93 cm.	0.91 cm.
Variations:	0.60–1.20 cm.	0.60–1.30 cm.	0.65–1.10 cm.	0.80–1.00 cm.

*This result may be partially due to the comparatively smaller number of negro male skulls represented in the figures.

The depth averages of these four groups are very uniform. But while in the white it is the female, in the black it is the male whose average depth is somewhat greater. The scales of variation are again much smaller in the negro.

According to these three measures, we see that the three dimensions of the fossa do not differ very much in their values. According to these figures the width of the fossa is its greatest, and the depth its least measure.

The average of the fossæ of the white male, is longer, broader, and slightly shallower than that of the white female, and also longer, broader and shallower than that of the male negro. This would tend to approach the types of the fossa in the negro male and the white female.

Of the negro male and female the pituitary fossa of the male is the longer, narrower and deeper.

These differences among the principal measures of the fossa can also be expressed by indices, but these present no special advantages.

These three measures (length, width and depth) form the constituents of the module and this reflects their combined character. We find the module of the pituitary fossa for each of the four series of skulls to be as follows:

	White Male.	White Female.	Negro Male.	Negro Female.
Averages:	1.057	1.006	1.056	1.062
Variations:	.867–1.167	.867–1.250	.967–1.200	.900–1.217

The figures express clearly that the fossæ of the males of the two human families are of almost identical volume. The fossa of the white female is slightly smaller than that of the white male, while in the negro there is a very small increase in size in favor of the female.

The variations of the module are interesting to observe. Their range is very much smaller than that of the indi-

vidual measures, which is a proof that the measures of the fossa largely compensate each other. Because of this quality of the module, it is of greater value than the individual measurements.

There remain to be pointed out the relations of the size of the pituitary fossa to the circumference of the skull. We would meet with disappointment if we should expect to find a regular correspondence of those two values. Nevertheless there is a certain correspondence, for as we proceed to larger skulls, generally speaking, the fossa, also, will be found larger. This point cannot be better illustrated than by giving here the module circumference relations in detail. I will arrange these cases without relation to sex or color, neither of which seems to make any difference in this point, beginning at the lowest and advancing to the highest circumference.

Circumf. Max.	Module of Pituitary Fossa.	Relation of Module to Circumf.
48.0 cm.	1.000 cm.	20.8 cm.
50.2 cm.	0.967 cm.	18.6 cm.
50.8 cm.	1.083 cm.	21.3 cm.
51.0 cm.	0.917 cm.	18.0 cm.
51.2 cm.	0.917 cm.	17.8 cm.
51.3 cm.	0.950 cm.	18.5 cm.
51.5 cm.	0.900 cm.	17.4 cm.
51.6 cm.	1.033 cm.	20.0 cm.
51.7 cm.	1.050 cm.	20.3 cm.
52.0 cm.	0.983 cm.	18.9 cm.
52.0 cm.	0.967 cm.	18.6 cm.
52.3 cm.	1.167 cm.	22.3 cm.
52.7 cm.	1.067 cm.	20.2 cm.
53.0 cm.	1.133 cm.	21.4 cm.
53.0 cm.	1.117 cm.	21.1 cm.
53.2 cm.	1.117 cm.	21.0 cm.
54.2 cm.	1.050 cm.	19.4 cm.
54.5 cm.	1.083 cm.	19.9 cm
55.0 cm.	1.017 cm.	18.5 cm.
56.0 cm.	1.133 cm.	20.2 cm.

Divided into groups of five, these figures give the following averages:

Circumference.	Average Module.	Average Relation of Module to Circum.
48.0–51.2 cm. incl.	0.977 cm.	19.3 cm.
51.3–52.0 cm. incl.	0.983 cm.	19.0 cm.
52.0–53.0 cm. incl.	1.090 cm.	20.7 cm.
53.2–56.0 cm. incl.	1.080 cm.	19.8 cm.

According to the above figures the average module, or the size of the pituitary fossa as represented by the modules, increases with the greater size of the skull, but apparently the increase ceases after the average size of the skull is passed. The maximum of the ratio of the module to the circumference corresponds to the maximum of the size of the fossa.

It is not possible to establish from the foregoing data any law of correspondence of the proportion of the fossa to the circumference of the skull. This will be appreciated by the accompanying drawing. (Plate III, Fig. 1).

The paper might be finished here were it not for a peculiar difference of a little structure adjoining the pituitary fossa, in the white and in the negro. I refer to the space bounded by the anterior and posterior olivary ridges and including the optic groove and the olivary eminence.

This space is, in general, very much narrower antero-posteriorly in the negro than in the white, and that in both sexes. The defect concerns especially the olivary eminence.

Following are the antero-posterior measures of this space:

	White Male.	White Female.	Negro Male.	Negro Female.
Averages:	0.562 cm.	0.611 cm.	0.425 cm.	0.386 cm.
Variations:	0.20–0.85 cm	0.30–0.85 cm.	0.25–0.70 cm.	0.10–0.70 cm.

The greater antero-posterior narrowness of the space in the negro is very evident. It can be expressed to a further advantage by the following curves. (Plate III, Fig. 2).

The significance of marked difference in the antero-posterior extent of the space containing the optic tract and the olivary eminence, in the white and the negro, is obscure, but some light may be thrown on it by futher investigations at autopsies.

The medical value of these measurements lies in the fact, that they represent the dimensions which the pituitary fossa may acquire, in individual directions as well as a whole, in the normal state. Should in a given case, and particularly in a white person, any individual measure of the fossa, taken with care and according to the rules laid down in this paper, markedly exceed the variations of the same measure here recorded, such a measure may safely be considered abnormal. On the other hand, no pituitary fossa can safely be considered as abnormal in size so long as its individual measure, and its module, are not above the variations of the same measures here recorded.

In an appendix will be found a reference list of the detail measures of the pituitary fossa on the four series of skulls examined.

APPENDIX.

The detail measurements of the four series of skulls:

SKULLS OF WHITE MALE ADULTS.—TABLE I.

No.	Diameter ant. post.	Width.	Depth.	Diameter later. bet. pts. of ant. clinoids.	Diameter a-post to ant. border of oliv. emin.	Distance bet. the two oliv. ridges.	Module. $\frac{W+L+D}{3}$	Circumf. of skull.	Relation of module to circ. $\frac{M \times 1000}{C}$
1	1.25 cm.	1.25 cm.	0.85 cm.	1.45 cm.	1.65 cm.	0.40 cm.	1.117 cm.	53.2 cm.	21.0 cm.
2	1.25	1.15	0.95	2.35	1.60	0.35	1.117	?	?
3	1.00	0.75	0.95	2.10	1.60	0.60	0.900	?	?
4	1.10	1.30	1.00	2.60	1.70	0.60	1.133	?	?
5	1.00	1.30	1.10	?	?	?	1.133	56.0	20.2
6	0.75	1.45	0.75	2.70	1.45	0.70	0.983	52.0	18.9
7	0.85	1.10	1.10	2.70	1.45	0.60	1.017	55.0	18.5
8	1.40	1.10	0.95	2.50	1.80	0.70	1.150	?	?
9	1.30	1.30	0.80	2.80	1.90	0.60	1.133	53.0	ab't 21.4
10	1.15	1.50	0.80	2.90	1.75	0.60	1.150	?	?
11	1.20	1.10	1.00	2.45	1.70	0.50	1.100	?	?
12	1.05	1.30	0.85	?	1.90	0.85	1.067	?	?
13	1.20	1.40	0.60	2.50	1.95	0.75	1.06	52.7	20.2
14	1.05	1.50	0.95	?	1.60	0.55	1.167	?	?
15	0.90	0.95	0.90	?	1.45	0.55	0.917	?	?
16	0.90	1.20	1.00	2.40	1.60	0.70	1.033	?	?
17	1.45	0.85	0.90	?	2.00	0.55	1.067	?	?
18	1.00	1.25	1.00	1.80	1 60	0.60	1.083	?	?
19	1.30	0.90	0.95	2.40	2.00	0.70	1.050	54.2	19.4
20	1.25	1.40	0.70	2.70	1.80	0.55	1.117	?	?
21	1.00	1.20	1.00	?	1.70	0.70	1.067	?	?
22	1.15	1.00	0.90	?	?	?	1.020	?	?
23	0.95	1.00	0.80	2.30	1.30	0.35	0.917	?	?
24	1.20	0.70	0.70	?	?	?	0.867	?	?
25	1.10	1.15	1.20	1.80	1.50	0.40	1.150	?	?
26	1.40	1.00	0.95	?	?	?	1.117	?	?
27	1.10	1.10	0.70	?	?	?	0.937	?	?
28	1.20	1.10	0.90	2.00	1.60	0.40	1.067	?	?
29	1.00	1.00	0.80	1.80	1.20	0.20	0.933	?	?
30	1.25	1.00	1.15	2.30	1.80	0.55	1.133	?	?

APPENDIX.—(*Continued*).

SKULLS OF WHITE FEMALE ADULTS.—TABLE II.

No.	Diameter ant. post.	Width.	Depth.	Diameter later. bet. pts. of ant. clinoids.	Diameter a-post. to ant. border of oliv. emin.	Length of olivary eminence.	Module. $\frac{W+L+D}{3}$	Circumf. of skull.	Relation of module to circ. $\frac{M \times 100}{C}$
1	0.90 cm.	1.00 cm.	0.70 cm.	2.00 cm.	1.70 cm.	0.80 cm.	0.867 cm.	?	?
2	1.15	1.50	1.10	2.60	2.00	0.85	1.250	?	?
3	0.80	1.00	0.90	2.20	1.45	0.65	0.900	51.5	17.4
4	0.80	1.10	0.90	?	1.40	0.60	0.933	?	?
5	1.00	1.35	0.80	2.45	1.55	0.55	1.050	51.7	20.3
6	1.15	1.10	0.60	1.75	1.60	0.45	0.950	51.3	18.5
7	0.95	1.10	0.70	?	1.65	0.70	0.917	?	?
8	0.90	1.00	1.20	?	1.50	0.60	1.033	?	?
9	1.30	0.95	0.85	?	1.90	0.60	1.033	51.6	20.0
10	1.15	0.85	0.90	2.40	1.90	0.75	0.967	50.2	18.6
11	0.90	0.90	0.95	?	1.20	0.30	0.917	?	?
12	0.80	0.80	1.15	?	1.50	0.70	0.917	51.0	18.0
13	0.90	1.25	0.95	?	1.45	0.55	1.033	?	?
14	1.05	0.90	1.10	?	1.60	0.55	1.017	?	?
15	1.05	1.00	1.00	?	1.90	0.85	1.017	?	?
16	0.90	1.25	0.95	2.30	1.55	0.65	1.033	?	?
17	0.75	1.00	1.00	?	1.35	0.55	0.917	?	?
18	0.95	0.90	0.90	2.15	1.60	0.65	0.917	?	?
19	1.05	1.20	1.10	2.40	1.45	0.40	1.083	49.0	22.0
20	0.75	1.20	0.80	2.60	1.20	0.54	0.917	51.2	17.8
21	1.10	1.30	0.85	2.70	1.70	0.60	1.083	50.8	21.3
22	1.15	1.10	1.25	?	1.50	0.35	1.167	?	?
23	1.15	1.10	1.00	?	1.80	0.65	1.083	?	?
24	1.30	1.10	0.75	2.35	2.15	0.85	1.050	50.5	20.8
25	1.20	0.85	1.00	?	?	?	1.017	51.0	19.9
26	0.90	1.15	1.30	2.15	1.50	0.60	1.117	?	?
27	1.00	1.20	0.75	?	1.65	0.65	0.983	ab't 50.7	ab't 19.4

APPENDIX.—(*Continued*).

SKULLS OF NEGRO MALE ADULTS.—TABLE III.

No.	Diameter ant. post.	Width.	Depth.	Diameter later. bet. pts. of ant. clinoids.	Diameter a-post to ant. border of oliv. emin.	Length of olivary eminence.	Module. $\frac{W+L+D}{3}$	Circumf. of skull.	Relation of module to circ. $\frac{(M\times 100)}{C}$
1	1.20 cm.	1.20 cm.	0.95 cm.	2.00 cm.	1.55 cm.	0.35 cm.	1.117 cm.	?	?
2	1.00	1.00	0.95	2.40	1.70	0.70	0.983	?	?
3	1.25	1.20	0.90	2.10	1.50	0.25	1.117	53.0	21.1
4	1.00	0.95	0.95	?	1.65	0.65	0.967	52.0	18.6
5	?	1.15	1.10	2.25	1.15	?	?	?	?
6	1.15	1.05	0.70	?	1.40	0.25	0.967	?	?
7	1.20	1.40	1.00	2.45	1.60	0.40	1.200	51.5	23.3
8	0.85	1.20	1.00	?	1.25	0.40	1.017	?	?
9	1.10	1.30	0.85	3.10	1.50	0.40	1.083	54.5	19.9

SKULLS OF NEGRO FEMALE ADULTS.—TABLE IV.

No.	Diameter ant. post.	Width.	Depth.	Diameter later. bet. pts. of ant. clinoids.	Diameter a-post. to ant. border of oliv. emin.	Length of olivary eminence.	Module. $\frac{W+L+D}{3}$	Circumf. of skull.	Relation of module to circ. $\frac{M\times 100}{C}$
1	0.80 cm.	1.00 cm.	0.90 cm.	2.25 cm.	1.20 cm.	0.40 cm.	0.900 cm.	?	?
2	1.00	1.00	0.90	2.20	1.20	0.20	0.967	?	?
3	0.85	1.30	0.85	2.20	1.30	0.45	1.000	48.0	20.8
4	1.10	1.55	1.00	2.60	1.80	0.70	1.217	49.5	24.6
5	1.40	1.30	0.80	2.30	1.95	0.55	1.167	52.3	22.3
6	1.00	1.00	1.00	2.25	1.10	0.10	1.000	?	?
7	1.30	1.30	0.95	?	1.60	0.30	1.183	?	?

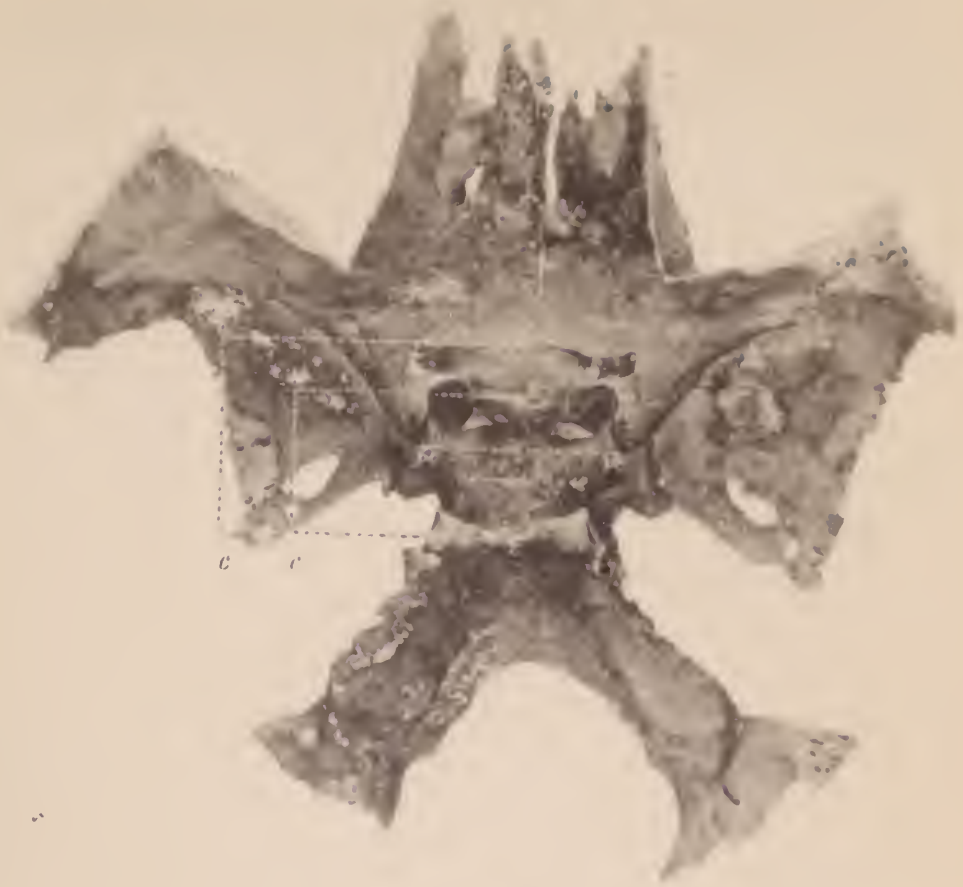


FIG. 1.

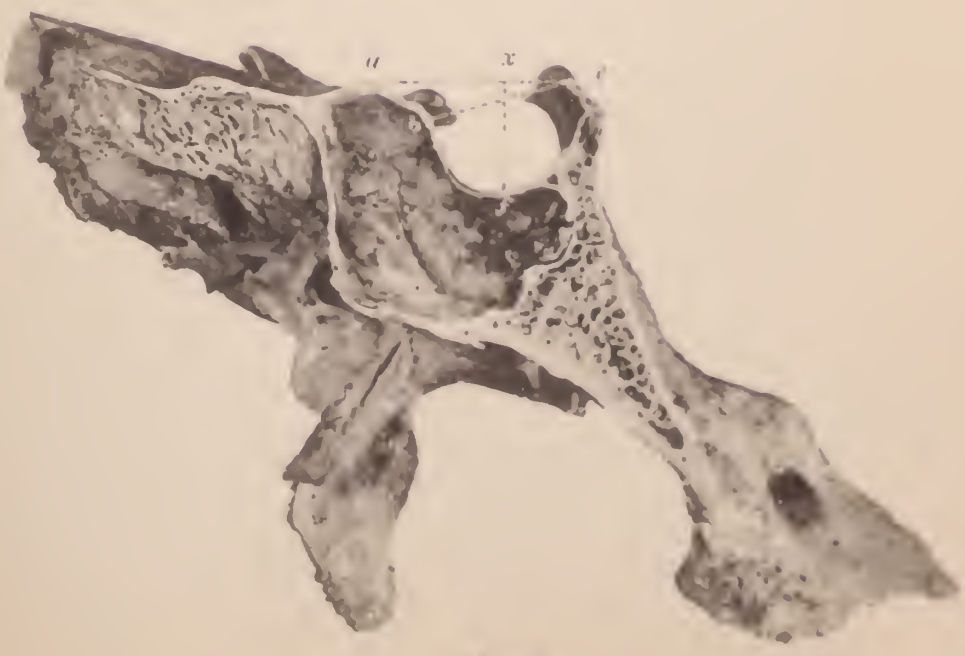


FIG. 2.

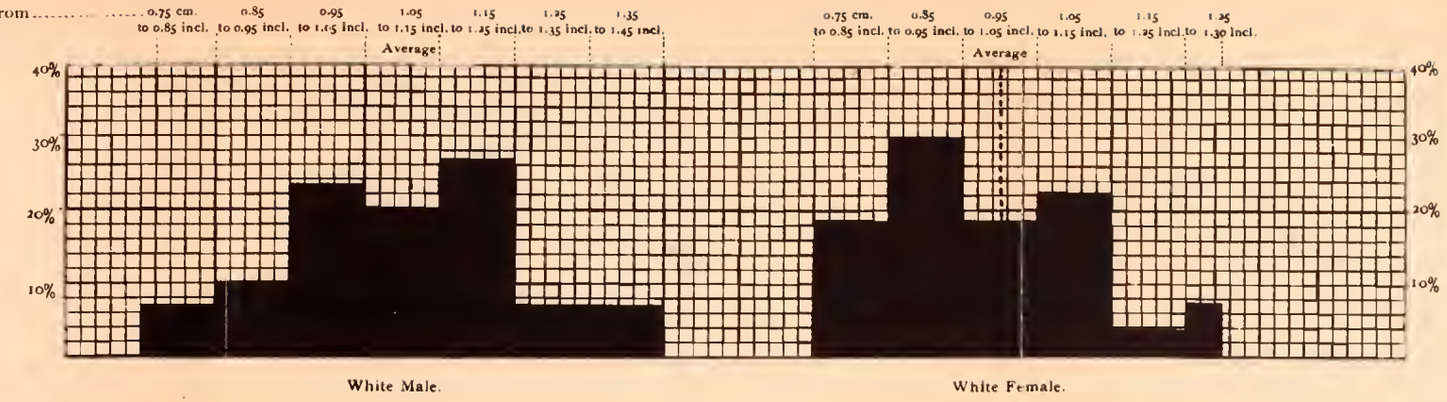


FIG. 1.—CURVES SHOWING THE PERCENTAGE OF FOSSAE WITHIN EACH *length* VARIATIONS OF 1 MM.

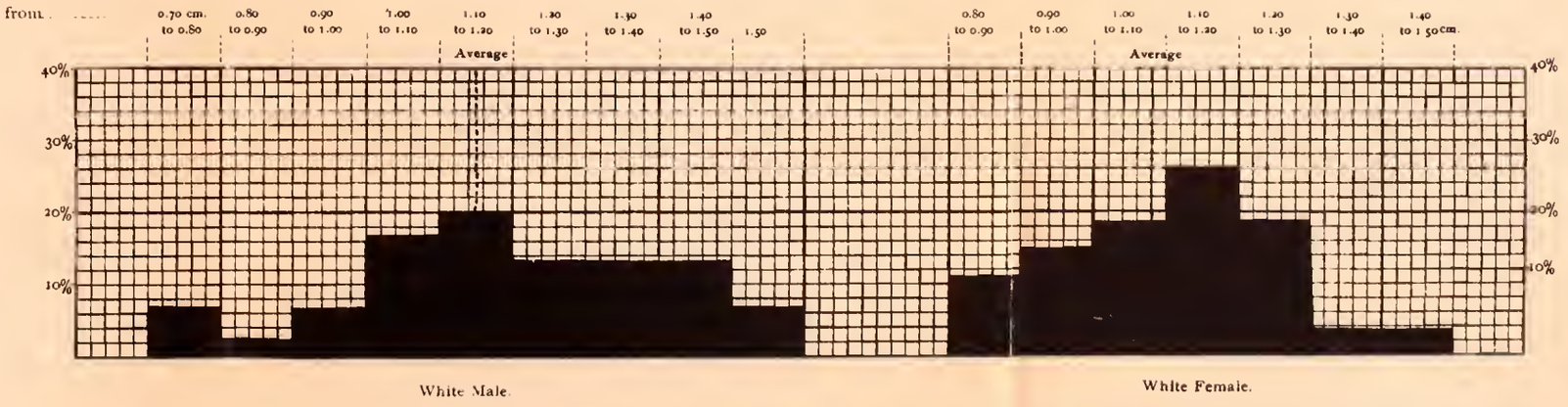


FIG. 2.—CURVES SHOWING THE PERCENTAGE OF FOSSAE WITHIN EACH *width* VARIATIONS OF 1 MM.

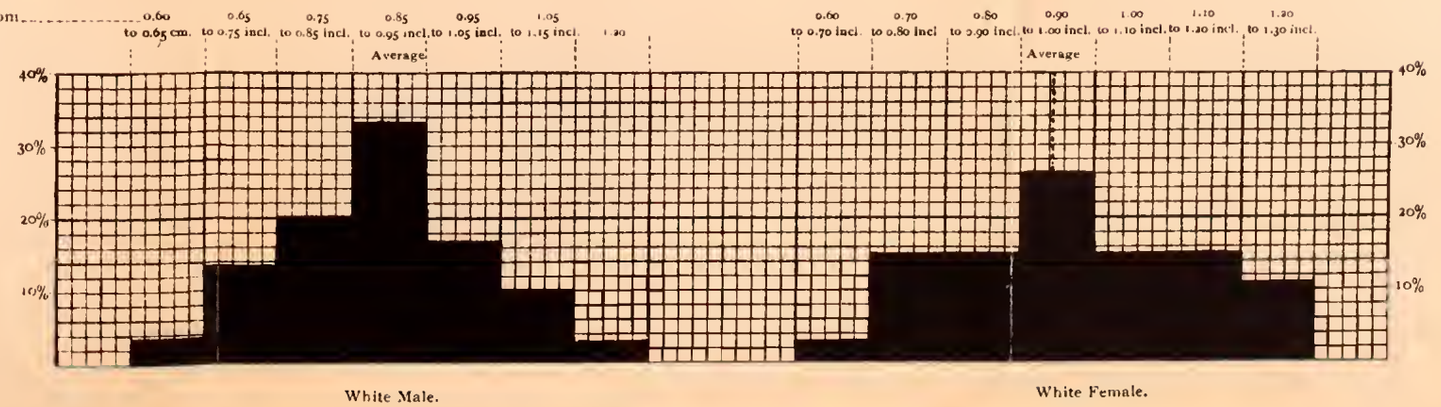


FIG. 3.—CURVES SHOWING THE PERCENTAGE OF FOSSAE WITHIN EACH *depth* VARIATIONS OF 1 MM.

FIG. 1.—RELATIONS OF THE MODULE OF THE PITUITARY FOSSA TO THE CIRCUMFERENCE OF THE SKULL.

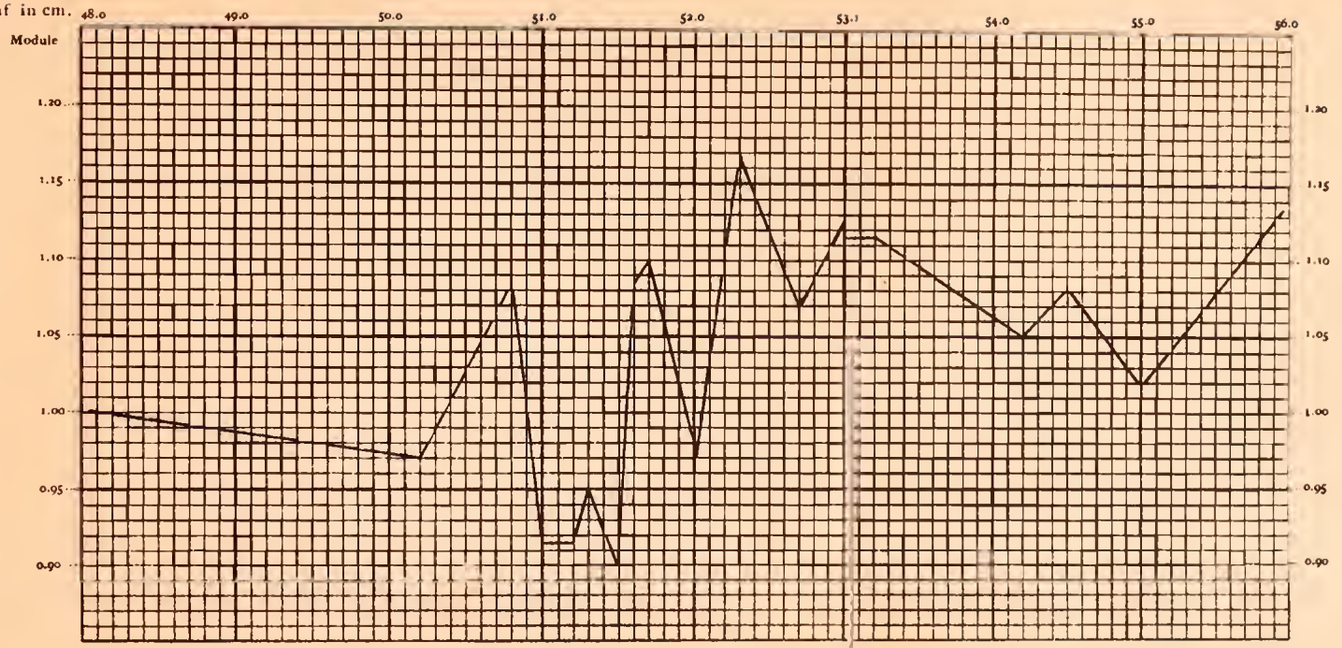
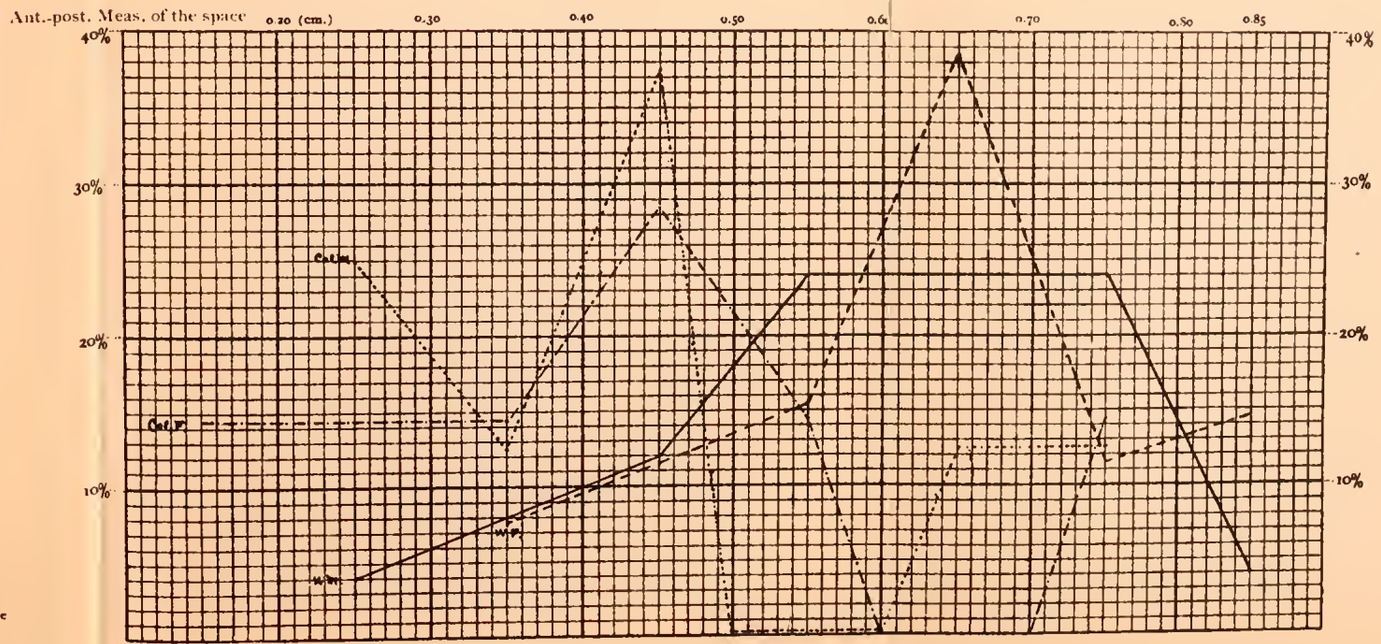


FIG. 2.—CURVES SHOWING THE DIFFERENCES IN THE ANTERO-POSTERIOR EXTENT OF THE SPACE INCLOSED WITHIN THE TWO OLIVARY RIDGES, IN FRONT OF THE PITUITARY FOSSA, BETWEEN THE WHITES AND THE NEGROES OF BOTH SEXES.



THE HELIOTYPE PRINTING CO., BOSTON.

A CASE OF EXCESSIVE DISTORTION OF THE OPTIC CHIASM IN ACROMEGALIA.

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New York.

[*From the Pathological Institute of the New York State Hospitals.*]

The history of this patient was first published by Dr. Isaac Adler in the *New-Yorker Medicinische Monatschrift* for May, 1888, she being at that time thirty-four years old and having well-marked acromegalia, without any eye symptoms. The autopsy, after her death at the Montefiore Home, November 19, 1898, was made by Dr. Harlow Brooks, and the findings are recorded by him on pages 524 *et seq.*, of this number.

From the hospital record the following note in regard to the ocular conditions was obtained.

February, 1897. Both optic discs pale; right field contracted on nasal, superior and inferior sides to 35°, on temporal side to 60°; left field slightly contracted. R. v=$\frac{20}{40}$; L. v=$\frac{20}{30}$.

Dr. Joseph Fraenkel, the resident physician, afterwards frequently examined the patient's visual fields to learn if bitemporal hemianopsia had developed, but the contraction, which increased somewhat, was always found to be concentric.

At the autopsy, after the pituitary body had been removed, the region of the chiasm presented the peculiar picture represented in Fig. 1; and some of those present were inclined to believe there had been a congenital absence of the chiasm,—a view which was supported by the fact that there had never been bitemporal hemianopsia, yet if a normally-formed chiasm had been divided anteroposteriorly, bitemporal hemianopsia must have resulted.

As the condition of the chiasm was so remarkable, it seemed advisable to examine carefully the entire visual tract, and through the courtesy of Dr. Adler and Dr. Fraenkel I was enabled to undertake this examination, which was carried out at the Pathological Institute of the New York State Hospitals.

The entire brain was put into ten per cent formol solution for a week, and then was divided into several parts, the region of the chiasm and that of the optic radiations being transferred to Müller's fluid, in order that Weigert's stain might be used.

The details of the examination of the various parts follow:

Eye.—The macular region of the right retina was imbedded in paraffin and cut in horizontal sections. In Nissl preparations post-mortem changes were found in the ganglion cells of the retina, but the cells were normal in number and in arrangement. In total horizontal sections of the posterior segment of the right eye after celloidin imbedding, the ganglion cells were found to extend normally to the extreme periphery of the retina on both temporal and nasal sides. The nerve-fibre layer of the retina appeared slightly thinner than normal, and the optic nerve was slightly reduced in size.

Cerebral Cortex.—A slice of cortex about the centre of the left calcarine fissure was imbedded in celloidin and cut in vertical sections. Stained by Nissl's method the cortical layers in the visual area seemed normal in every respect.

Optic Radiation.—Vertical sections through the entire left hemisphere in the region of the optic radiation, when stained by the Weigert-Pal method exhibited no signs of degeneration of the nerve fibres.

Chiasm.—The enlarged pituitary body measured three cm. antero-posteriorly and 2.7 cm. in depth. It lay in the position indicated by the fine dotted line in the diagram,

Fig. 2. When removed, it was torn away from an anterior attachment to a flat bit of tissue one cm. square, P. Figs. 2 and 3. This, when examined microscopically, proved to be a portion of the pituitary body covered by its dense fibrous capsule, which had become adherent to the chiasm. Both optic nerves and their posterior continuations were flattened and small, the portion corresponding to the left tract seeming to be particularly small.

No trace of a chiasm was seen. The right optic nerve presented a process 1 cm. long and 2 mm. in diameter, which ran nearly at a right angle from the inner margin of the nerve toward the median line. The right tract was flattened and, in the region where the chiasm should be, apparently amalgamated with the portion of the brain on which it lay.

Serial sections were made through the entire region of the chiasm after the tissues had been divided previously in the median line so that each optic nerve with its posterior continuation was sectioned separately. A number of these sections were stained with Wolters' hæmatoxylin and differentiated by Pal's method.

At A, Figs. 2 and 4, the right nerve was found to be flattened and degenerated below and to the inner side, where the medullary sheaths of the fibres did not take the stain. Sections at B, Figs. 2 and 4, showed degeneration below and to the inner side of the nerve, and the process from the nerve was found to consist of connective and glia tissue without any normal nerve fibres. Sections at C, Figs. 2 and 4, showed that the crossed fibres in the chiasm had not been altogether destroyed, but that in a flattened vascular mass of connective and glia tissue a few normal, dark staining fibres still remained. Sections at D, Figs. 2 and 4, showed a considerable number of crossing fibres stained normally. Sections at E, Figs. 2 and 4, revealed but few normal crossing fibres, and sections at F, Figs. 2 and 4, quite posterior to the chiasm, showed some degeneration of the inner and lower margins of the optic tract.

Serial sections of the left side of the chiasm revealed

conditions very similar to those on the right. Sections at G, Figs. 2 and 4, showed the nerve to be degenerated in its central portions and below and to the inner side. Sections at H, Figs. 2 and 4, revealed a normal nerve and a few normally stained crossing fibres in the chiasm. Sections at I, Figs. 2 and 4, contained a considerable number of normal nerve fibres in the region of the chiasm. Sections at J, Figs. 2 and 4, showed a lesser number of normal nerve fibres in the crossed bundles of the chiasm, and the crossing fibres in the nerve were degenerated. Sections at K, Figs. 2 and 4, at the beginning of the tract, showed some degeneration in the entire periphery of the tract. Sections at L, Figs. 2 and 4, through the optic tract, far back, showed a degeneration of the upper, outer and inner portions of the tract.

A section of the right nerve, stained by van Gieson's method, is represented in Fig. 3, (at C, Fig. 2). The chiasm here consists of some connective and considerable glia tissue, with a great number of vessels which naturally lie close together since many of the medullated nerve fibres have disappeared. Resting on the chiasm at this point but not directly adherent to it, is the portion of the pituitary tumor which was torn off in removal. (P. Figs. 2 and 3).

Sections stained by van Gieson's method did not exhibit either round-celled infiltration or increase in connective tissue anywhere in the optic nerves, chiasm, or tracts.

RÉSUMÉ.

To sum up, the chiasm was flattened out, both antero-posteriorly and laterally, into a thin mass about 2.5 cm. square, and a certain number of its nerve fibres were degenerated. The optic nerves were not compressed by bony constriction of the optic foramina, and the degeneration, therefore, was due to the pressure exerted on the chiasm and tracts by the pituitary body. The degeneration of the nerve fibres was more marked in the anterior and posterior portions of the chiasm than in

the centre. Anteriorly a small bundle of fibres apparently had become entirely separated from the rest of the chiasm and had eventually been cut through, leaving the atrophic process seen at B, Figs. 2 and 4.

The degenerated fibres were, in the main, fibres of the crossed bundles together with a few fibres belonging to the uncrossed bundles, and lying particularly in the lower portion of the chiasm, where they were directly compressed. The degeneration of the fibres had extended posteriorly through the tracts (but not beyond the basal ganglia into the optic radiations), and anteriorly through the nerves to the retina, but the ganglion cells of the retina were still present. There were no signs of interstitial inflammation that would indicate previous neuritis.

The remarkable feature of the case is that, notwithstanding the great and unusual distortion of the chiasm, there should have been so little degeneration of the fibres in the optic nerves and tracts, and so slight a disturbance in vision.

GENERAL CONSIDERATIONS.

Visual disturbances have been found in about fifty per cent of the one hundred and seventy-five cases of acromegalia that have been reported. These disturbances may not come on until late in the disease, as in the present case, and they may be absent even when there is considerable enlargement of the pituitary body, as has been demonstrated several times at autopsies. On the other hand, as I have myself twice seen, these disturbances may be among the earliest symptoms of acromegalia, and their detection may then be absolutely essential to a diagnosis.

In rather more than half the cases in which there is disturbance of vision, there is a diminution of central vision

with an irregularly concentric contraction of both visual fields. In a somewhat smaller percentage, there is not much diminution of central vision, but there is a hemianopic defect in the temporal half of each visual field. In half a dozen cases homonymous hemianopsia has been found, and in one case binasal hemianopsia.

Usually, there is some inflammation of the optic nerves, varying from a slight neuritis to a papillitis or choked disc, but in a considerable number of cases the optic discs present the picture of simple atrophy of the optic nerves.

When the enlarged pituitary body spreads out over the base of the chiasm there will be uniform pressure on the chiasm, and the visual fields may progressively become contracted on all sides, until blindness ensues.

When the growth lies farther back, compressing the chiasm from behind and the optic tracts from within, at first only the crossed bundles of the chiasm will be affected, and various sorts of bitemporal hemianopsia will be found. Thus, the fields may be normal for white test objects, while for colors the whole or a part of each temporal field may be wanting. Tests made with one cm.-square patches of gray of various intensities on white backgrounds will often show that the entire half of the visual field is wanting for pale gray, but that only a small portion of the field is wanting for medium gray, indicating different degrees of interference with conduction in different bundles of fibres. Again, with complete bitemporal hemianopsia for colors and for pale gray patches, each temporal field may present also a small absolute scotoma for white.

Finally, and this is the characteristic field for acromegalia, there may be absolute bitemporal hemianopsia,

when even white is not recognized in the temporal half of each field. With the further growth of the tumor and the successive involvement of the various portions of the chiasm, usually the infero-nasal quadrant of one field will be lost, then the infero-nasal quadrant of the other, and then the supero-nasal quadrant of the first—this eye then becoming totally blind. The supero-nasal quadrant of the second field will still remain for a time, but this, also, will eventually be lost.

When the pressure affects one tract only, a right or left homonymous hemianopsia (absolute or for colors) results, but this has usually soon become complicated with a defect in the temporal half of that field whose nasal half was affected in the beginning, thus indicating the existence of pressure upon the chiasm as well as upon one tract, and locating the source of pressure in the pituitary body.

As the examination of the visual fields shows with such precision exactly what bundles of fibres in the chiasm have suffered in cases of compression from tumors of the hypophysis cerebri, observers hitherto have been content to accept the records of the perimeter as sufficient without devoting much attention to microscopic examinations of the chiasm; and the present contribution is offered as showing how little the nerve fibres may suffer from excessive compression provided that optic neuritis is not set up.

EXPLANATION OF FIGURES.

Figure 1.—Region of chiasm, natural size. [Bosse, del.]

Figure 2.—Diagram of chiasm showing locations and directions of sections represented in Figs. 3 and 4. [Bosse, del.]

Figure 3.—Section at C, Fig. 2, Van Gieson's stain. Magnified ten diameters. P, a bit of pituitary tumor with its capsule. [Bosse, del.]

Figure 4.—Serial sections of chiasm, Wolters-Pal modification of Weigert's hæmatoxylin stain. See diagram Fig. 2 for location of sections, the lettering being alike in Figs. 2 and 4. [Leaming, photo.]

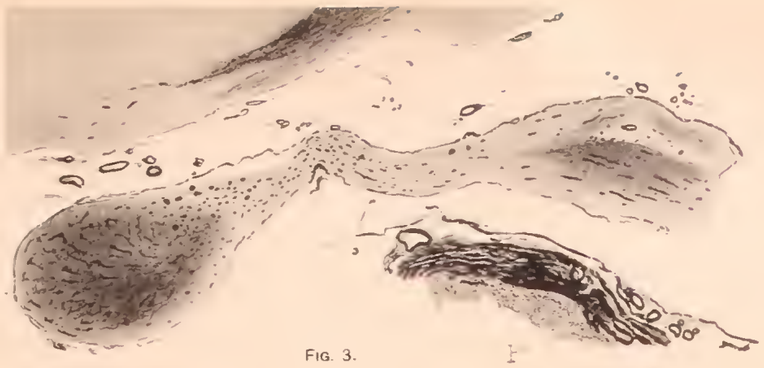

FIG. 3.

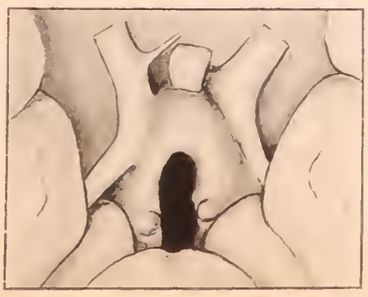

FIG. 1.

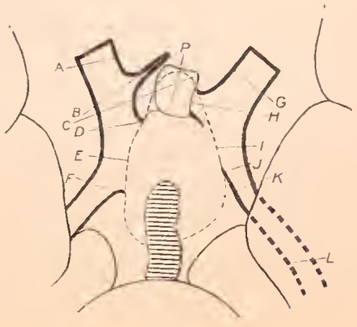

FIG. 2.

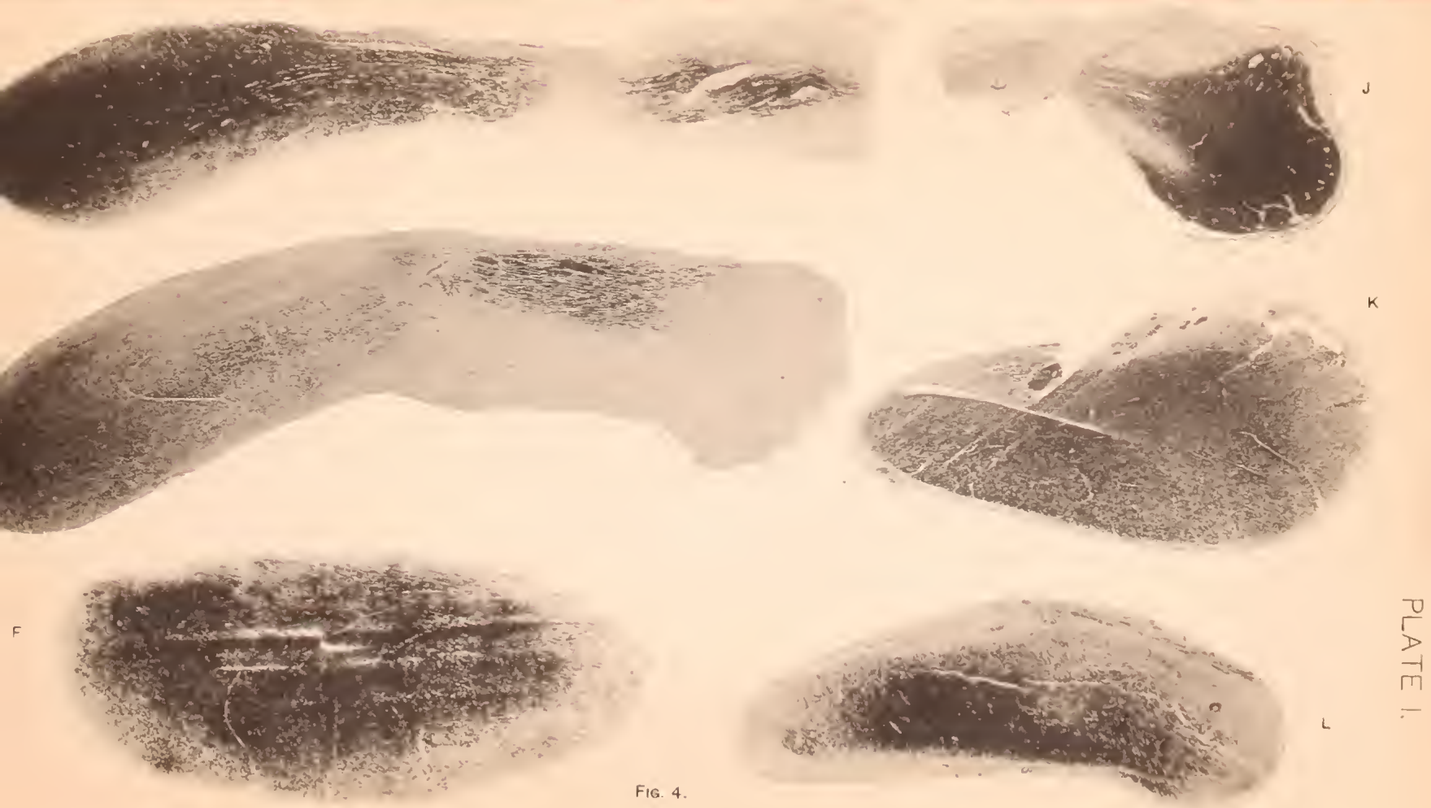

FIG. 4.

REPORT OF TWO CASES OF ACROMEGALIA WITH REMARKS UPON THE MENTAL CONDITION IN THIS DISEASE.

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At the last meeting of the British Medico-Psychological Association Dr. David Blair read a paper entitled "Acromegaly with Insanity,"* in which he describes a case of persecutory mania associated with acromegalia in a woman. He calls attention to the rarity of this disease in asylums and says that but three cases have come to his knowledge, one in England and two on the Continent.† It has seemed, therefore, an appropriate occasion to review, briefly, a case published in the Eighth Annual Report of the St. Lawrence State Hospital, December, 1894, under the title "Mental Enfeeblement in Acromegaly."

This man, Case No. 1372, was arrested in 1885, in one of the cities in this State as a tramp, and was committed to the county almshouse. When his true mental condition became apparent, he was examined and duly committed to a hospital for the insane. The certificate of lunacy throws but little light on his mental condition at that time; it states that he wandered about aimlessly and was not able to take care of himself. He was described as about fifty years of age, married, a blacksmith by trade, and could speak no language except German. The

* *Journal of Mental Science*, April, 1899.

† In the discussion which followed the reading of this paper Dr. Whitcombe mentioned a case of acromegalia with epilepsy in a young man of 28 who died in the Winson Green Asylum.

notes at this time show that he was a mild case of gradually increasing dementia. There is no mention of delusions or hallucinations, but it was noted that he was irritable, especially when unemployed, and would not permit tight bands in his clothing, and always kept his shirt unbuttoned at the neck. His peculiar physiognomy was noted but not described, and there was no record of the appearance of his hands or feet. He was transferred to the St. Lawrence State Hospital January 18th, 1894. He was found to be a man below the medium height, but of large frame and thick set, with a marked cervico-dorsal kyphosis, which projected his head forward until the chin almost touched the sternum. A line drawn from the occipital protuberance to the twelfth dorsal vertebra described a fairly regular curve. The skull, thickly covered with stiff, dark hair, at first glance appeared small, but this was due largely to the contrast with the large face and lower jaw. The forehead was low and deeply furrowed with wrinkles; the ears were large and prominent and the lobes poorly developed. His prominent brows gave the eyes the appearance of being deeply set and small, while the nose was large and broad. The lower portion of the face was prognathous, which, together with the everted lower lip, gave the face a striking and characteristic appearance. The upper teeth were all missing, the lower were separated by distinct spaces. His hands and feet were thick, broad and presented the characteristic appearance which is now well understood. His expression was peculiarly sad and pathetic, due in a large measure to the everted lower lip, which, with his attitude, resembled the profound dementia sometimes seen in gross disease of the brain. His speech was thick and guttural and his words were imperfectly uttered, particularly the

linguals. Little could be made out by questioning him; he made his wants known as briefly as possible and avoided all other speech. His memory for events long past seemed to be a complete blank, but for more recent occurrences it was better. He had a pretty fair appreciation of time and place, he was careful in his habits and industrious and worked daily at manual labor without more than ordinary fatigue, and was fond of exhibiting his strength, which was considerable. His appetite was very large and he drank considerable quantities of water daily. He perspired about as much as the average person. The quantity of urine in twenty-four hours, when he was idle, was about 1½ litres, of which the following examination was noted: acid, specific gravity, 1030; urea, less than normal; albumen and sugar, negative.

He died on the 11th of December, 1894, at 8 P. M., after a brief and acute attack of peritonitis. The autopsy was held at 11 A. M. December 12th.

External appearance of the cadaver was that of a well nourished man about 50 years of age; the abdomen was distended; peculiarities of appearance as described above.

Weight of brain, 49½ oz.; liver, 59 oz.; spleen, 7⅞ oz.; right kidney, 5½ oz.; left kidney, 4⅛ oz.; pituitary body, 10½ grains.

The skull was thickened throughout its entire circumference, the dura white and glistening, the pia was free from opacity or thickening and stripped readily. The membranes were apparently free from disease as were the vessels, with the exception of the internal carotids which were thickened. The brain was compact, of good weight and firm, the ventricles contained but little fluid. The pituitary body was appreciably increased in size, the following measurements were taken: Transverse diameter,

5/8 inch; antero-posterior, 3/8 inch; vertical, 1/4 inch. The sella turcica presented a little posteriorly to its centre a circumscribed depression distinctly marked.

The lungs were normal save for a moderate degree of congestion; the heart was firmly contracted, the valves competent and free from thickening, the muscular substance firm and of normal appearance.

The intestines were distended with flatus, large coils protruded when the peritoneum was divided, they were of a deep red color and the inflammation extended also to the parietal peritoneum. In the right iliac region the intestines were matted together by old and strong adhesions; the appendix was not easily found; it was closely adherent to the cæcum and was much deformed and shared in the general inflammation, but did not seem to be the original focus. The abdominal cavity contained serum and pus, and patches of lymph could be seen here and there. The kidneys were congested but otherwise normal.

This man came under observation too late to observe his mental condition during the height of the attack. When first seen he had apparently reached the terminal stages and was unable to remember his past life, or to converse intelligently regarding his present condition.

For the facts of the following case, as well as for the opportunity of examining him, I am indebted to Dr. G. C. Madill of Ogdensburg, who had made very careful notes of the case when it first came under his observation two years ago.

Case No. II.—A. W.—Age forty-four; single; born in New York State. His mother died of dropsy and his father of pneumonia. One brother also died of pneumonia. Other brothers and sisters, eight in number, are alive and in good health. They present none of the

peculiarities noted in the patient, nor have any been observed in any branch of the family. The brothers and sisters older and younger than the patient are more intelligent than he. He has worked as a fireman and always considered himself healthy except as will be noted below. He has used liquor moderately until about four years ago, since which time he claims to have taken nothing. He has never had a serious illness, but sustained a fracture of one arm about nine months ago, which was properly cared for and resulted in a good union. He has been subject to epilepsy since the age of seventeen; the first seizure was brought on by fright and they have occurred since every month or two, though he has gone as long as six months without one. The fits are preceded for about ten minutes by a buzzing sound in his head which increases in intensity until he loses consciousness for several minutes, and then arouses but is confused and dull for some minutes afterward. Frequently there are no convulsive movements at all, but his brother says there have been attacks during which the face was drawn convulsively towards the left shoulder. It is impossible to fix exactly the beginning of the change in his appearance; his own statements are unreliable, but it is probable that his hands and feet began to enlarge about eight or ten years ago; at that time he wore No. 8 shoes; when first seen by Dr. Madill he wore No. 10, and he now wears No. 11. The patient thinks his voice began to grow coarse before the change in his hands began, while his brother thinks it was subsequently.

About three years ago the patient noticed that his health was not as good as formerly. He began to have headaches which increased in frequency until they were almost constant. The pain extended around his head about the

level of the forehead; there were also pains in other parts of his body, but especially in the knees and back. He did not feel able to work as well as formerly and was breathless on exertion.* His gait is awkward and rolling like that of a sailor; he has difficulty in putting on and taking off his coat; when buttoning his shirt collar he has to use both hands and it takes him a long time. It was noticed that the bands of his clothing were quite loose, and when questioned about it he said that anything tight about his neck gave him a feeling of burning and suffocation through the chest. He bears cold well and has never found it necessary to wear gloves. His appetite is good and he is troubled more or less with thirst, drinking more than the men with whom he works. His voice has been changed for probably eight or ten years. It increased in depth gradually and is now deep, coarse and husky. His articulation is defective, but it consists only in a slurring of his words. The tongue is broad and thick, but he uses it fairly well, and has observed some stiffness in his lips so that he is now unable to whistle. His chest is large and massive and he has a well pronounced cervico-dorsal kyphosis, though it is not extreme. His breathlessness upon exertion has already been referred to. The bones of the trunk are large and strong. His height is five feet seven inches, and he weighs, at the present time, two hundred and twelve pounds. There seems to be no superfluous fat upon his body. The left knee is larger than the right by more than one inch. The enlargement is mainly of the outer condyle of the femur, which is about twice the size of the other. The knee has never been injured and he was not

*He has not worked steadily through the spring and summer and thinks these symptoms are in consequence less annoying.

aware of the difference until it was pointed out to him. The bones of the leg are symmetrical. The feet are large and broad, but the increase in size is particularly in their thickness. The sole of each is made up of an enormous pad which extends from the heel toward the toes. The arch, contrary to expectation, was found pretty well defined. The breadth of the foot at the heel is 3¼ inches and, at the base of the toes, the breadth is 4⅝ inches. The skin has no unusual color or quality. The quantity of hair is normal; he has a rather heavy growth of hair upon his face, and that upon his head is coarse and partly gray.

He appears to be feeble-minded. His memory particularly is defective. This was clearly shown by comparing the statements he made to Dr. Madill two years ago with the answers he gave to the same questions when examined by me. He appears to have very little idea of time. There is sometimes a difference of more than ten years in his two accounts of the appearance of some of his symptoms. He said at one time that his voice began to change when he was thirty years of age, and at another time said it began four years ago. In almost every instance he would become confused when trying to remember events happening several years ago. He acknowledges that he finds it difficult to remember the names of his acquaintances, and also their faces. This is evidently becoming more marked in recent years.

His brother told me that A. W. was never able to learn anything at school, and is to-day illiterate. He also failed to learn the trade of wheelwright, which his brother now follows. His brothers and sisters are said to live in comfortable circumstances, but the patient has never saved anything. How much of this dulness is properly to be

attributed to his epilepsy and how much to acromegalia is not easy to decide. His convulsions have never been frequent and during the past two years he has had fewer seizures than formerly, while his loss of memory for names and faces seems to be growing worse.

It seems to me that sufficient attention has not been given to mental symptoms in this disease. It is true that while in the early stages the acromegalic process has little or nothing to do with the nervous system, more or less mental failure occurs in the majority of cases sooner or later and complications of nervous disease are sufficiently common to attract attention. It seems that in many of the cases there is a mild form of dementia which shows itself in a placid disposition and occasional attacks of irritability when disturbed or interfered with. The case reported by Dr. Blair differs from these in that a well-defined attack of insanity occurred and that delusions and hallucinations were present which might reasonably be attributed to the disease. In both of the cases that have come under my observation, there has been an intolerance of tight bands in the clothing, which was explained by one of the patients as giving him a feeling of suffocation and burning in the chest. It is not unreasonable to believe that a similar sensation was experienced by Dr. Blair's patient who evolved from this sensation the delusion that she was being suffocated by gas.

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